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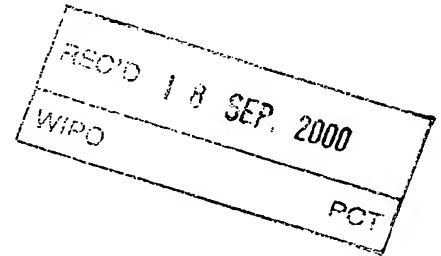
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Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Anmeldung.

München, den 08. Juni 2000
Deutsches Patent- und Markenamt
Der Präsident
Im Auftrag

Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren

Die vorliegende Erfindung betrifft Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren, sowie die entsprechenden Enzyme per se.

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Spinosyne stellen eine neue Gruppe von makrolidischen Verbindungen dar, die aus dem Actinomyceten *Saccharopolyspora spinosa* isoliert worden sind (Mertz und Yao, 1990). Sie werden zur Bekämpfung von Insekten eingesetzt (WO 97/00265, WO 94/20518, WO 93/09126, US 5670364, US 5362634, US 5227295, US 5202242). Spinosyne zeigen eine starke insektizide, jedoch keine antibakterielle Aktivität, wodurch sie von den konventionellen Makroliden, wie Tylosin, Spiramycin und Erythromycin, die keine insektizide, jedoch antimikrobielle Wirksamkeit aufweisen, unterscheidbar sind.

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Die Struktur der Spinosyne setzt sich zusammen aus einem tetracyclischen Polyketidgrundgerüst (Aglycon) mit einem 12-gliedrigen Makrolidring und einem 5,6,5-cis-anti-trans-Tricyclus, sowie einem D-Forosamin- und einem 2,3,4-Tri-O-Methyl-L-Rhamnose-Zuckeranteil (Kirst et al., 1991). Mehr als 20 verschiedene natürliche Spinosyn-Derivate, der sogenannte A83543 Komplex, ist bisher beschrieben worden (WO 97/00265, WO 94/20518, WO 93/09126). Diese Derivate variieren in der Substitution von einer oder einigen Methylgruppen am tetracyclischen Grundgerüst, am Forosamin- oder am Tri-Methyl-Rhamnose-Zuckeranteil. Ein 17-Pseudoaglycon, dem der Forosamin-Zuckeranteil fehlt, ist ebenfalls aus Kulturbrühen von *S. spinosa* isoliert worden.

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Die Hauptkomponenten des von *S. spinosa* gebildeten A83543 Komplexes stellen die Varianten Spinosyn A und Spinosyn D dar, die die wesentlichen Bestandteile des Produktes Spinosad darstellen (vgl. Pesticide Manual, British Crop Protection Council, 11th Ed., 1997, Seite 1272 und Dow Elanco trade magazine Down to Earth, Vol. 52, NO.: 1, 1997 und die darin zitierte Literatur).

Aufbauend auf Untersuchungen zum Einbau von C^{13} -markiertem Acetat, Propionat, Butyrat oder Isobutytrat konnte gezeigt werden, dass die Biosynthese von A83543 einem Polyketid-Biosyntheseweg folgt (Nakatsukasa et al., 1990). Polyketide werden durch multifunktionelle Enzyme, den sog. Polyketidsynthasen (PKS's) aus kurz-

5 kettigen Säurebausteinen wie Acetat, Propionat oder Butyrat aufgebaut. Ähnlich wie die verwandten Fettsäuresynthasen (FAS's) katalysieren sie decarboxylierende Polykondensationsschritte der als CoA-Thioester aktivierten Bausteine. Während FAS's nach jedem Kondensationsschritt eine vollständige Reduktion der intermediär an der wachsenden Polyketidkette entstehenden β -Oxoester durch Ketoreduktion,

10 Dehydratation und Enoylreduktion katalysieren, können PKS's bestimmte Reduktionsschritte auslassen. Modulare Typ I PKS's bestehen aus einem oder mehreren großen multifunktionalen Proteinen. Iterative Typ II PKS's stellen dagegen einen Komplex aus weitgehend monofunktionalen Proteinen dar.

15 Die enzymatischen Aktivitäten von modularen Typ I PKS's lassen sich zu sogenannten Modulen zusammenfassen. Hierbei trägt ein Modul eine Anordnung von drei enzymkatalytisch aktiven Domänen, die zu einer Verlängerung der wachsenden Polyketidkette um eine biosynthetische Verlängerungseinheit führen. Bei diesen Domänen handelt es sich um eine β -Ketoacyl:Acyl Carrier Protein

20 Synthase-Domäne, eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl Carrier Protein-Domäne. Ein Modul kann auch eine Ketoreduktase-, eine Dehydratase-, eine Enoylreduktase- und eine Thioesterase-Domäne tragen. Ein sog. Ladungsmodul, das am Beginn der Biosynthese steht kann von den genannten Domänen lediglich eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl-Carrier Protein-Domäne tragen,

25 sowie eine enzymatisch inaktive β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne. Eine Polyketidsynthase-Domäne umfasst jeweils eine dieser genannten enzymatischen Aktivitäten.

Aufgrund der potenten insektiziden Wirkung sowie der bemerkenswerten Struktur

30 der Spinosyne besteht ein großes Interesse, die genetischen Informationen für deren Biosynthese zu entschlüsseln.

Gegenstand der Erfindung sind Nucleinsäuren, welche zumindest eine Region umfassen, die für eine Enzymaktivität codiert, welche an der Biosynthese von Spinosynen beteiligt ist.

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Die vorliegende Erfindung stellt ein Cluster von offenen Leserahmen (ORF's) bereit, deren Translationsprodukte an der Biosynthese von Spinosynen beteiligt sind. Weiterhin werden zusätzliche Gene bzw. ORF's bereitgestellt, die außerhalb des ca. 120 kb großen Spinosyn-Biosyntheseclusters liegen, und deren Translationsprodukte an der Rhamnose-Zuckerbiosynthese beteiligt sind.

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Bei den erfindungsgemäßen Nucleinsäuren handelt es sich insbesondere um einzelsträngige oder doppelsträngige Desoxyribonucleinsäuren (DNA) oder Ribonucleinsäuren (RNA). Bevorzugte Ausführungsformen sind Fragmente genomischer DNA und cDNA's.

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Der Ausdruck "zumindest eine Region", wie er hierin verwendet wird, bedeutet, dass die erfindungsgemäße Nucleinsäure eine oder mehrere Sequenzen umfassen kann, welche jeweils für einzelne Aktivitäten codieren, die Schritte bei der Synthese von Spinosynen durchführen. Es werden demnach auch Nucleinsäuren als erfindungsgemäß betrachtet, die nur für eine einzige Enzymaktivität der Spinosyn-Biosynthese codieren.

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Der Ausdruck "Enzymaktivität", wie er hierin verwendet wird, bedeutet, dass ausgehend von den hierin betrachteten Nucleinsäuren zumindest derjenige Teil eines vollständigen Enzyms exprimiert werden kann, der noch die Katalyseeigenschaften des Enzyms ausübt.

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Insbesondere codieren die erfindungsgemäßen Nucleinsäuren für Enzymaktivitäten von Polyketidsynthasen, Methyltransferasen, Epimerasen, Glycosyltransferasen,

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Aminotransferasen, Dimethyltransferasen, Reduktasen, Dehydratasen und/oder Cyclisierungsenzymen.

Bevorzugt handelt es sich bei den erfindungsgemäßen Nucleinsäuren um DNA-Fragmente, die genomischer DNA von *S. spinosa* entsprechen.

Besonders bevorzugt umfassen die erfindungsgemäßen Nucleinsäuren zumindest eine Sequenz ausgewählt aus

- (a) den Sequenzen gemäß SEQ ID NOS: 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 52 oder 54,
- (b) zumindest 14 Basenpaare langen Teilsequenzen der unter (a) definierten Sequenzen,
- (c) Sequenzen, welche an die unter (a) definierten Sequenzen hybridisieren,
- (d) Sequenzen, welche eine zumindest 70 %ige, bevorzugt eine 80 %ige, besonders bevorzugt eine 90 %ige Identität zu den unter (a) definierten Sequenzen aufweisen,
- (e) Sequenzen, welche zu den unter (a) definierten Sequenzen komplementär sind, und
- (f) Sequenzen, welche aufgrund der Degeneriertheit des genetischen Codes für dieselbe Aminosäuresequenz kodieren wie die unter (a) bis (d) definierten Sequenzen.

Der Ausdruck "hybridisieren", wie er hierin verwendet wird, beschreibt den Vorgang, bei welchem ein einzelsträngiges Nucleinsäuremolekül mit einem komplementären Strang eine Basenpaarung eingeht. Auf diese Weise können beispielsweise ausgehend von genomischer DNA aus Organismen, die phylogenetisch mit *S. spinosa* verwandt sind und die Fähigkeit der Biosynthese von Spinosynen besitzen, DNA-Fragmente isoliert werden, welche dieselben Eigenschaften wie die aus *S. spinosa* isolierten Fragmente aufweisen.

Bevorzugte Hybridisierungsbedingungen sind nachstehend angegeben: Hybridisierungslösung: 5 x SSC; Blocking Reagents (Roche Diagnostics GmbH, Mannheim, Deutschland), 1 %; N-Lauroylsarcosin, 0.1 %; SDS (Sodiumdodecylsulfate) 0.02 %; Hybridisierungstemperatur: 60°C; erster Waschschrift: 2 x SSC bei 60°C; zweiter Waschschrift: 2 x SSC bei 60°C; bevorzugt zweiter Waschschrift: 0.5 x SSC bei 60°C; besonders bevorzugt zweiter Waschschrift: 0.2 x SSC bei 60°C.

Der Grad der Identität der Nucleinsäuren wird vorzugsweise bestimmt mit Hilfe des Programms GAP aus dem Programmpaket GCG (Devereux et al., 1984), Version 9.1 unter Standardeinstellungen.

Besonders hervorgehoben werden Nucleinsäuren, die

- (1) entweder alle Sequenzen, die für Schritte der Forosamin- und Trimethyl-Rhamnose-Biosynthese codieren, umfassen, insbesondere die Sequenzen gemäß SEQ ID NOS: 4 und 51, oder
- (2) alle Sequenzen, die für Schritte der Polyketidsynthese codieren, umfassen, insbesondere die Sequenzen gemäß SEQ ID NOS: 5 und 6, oder
- (3) alle Sequenzen, die für alle Schritte der Forosamin-, Trimethyl-Rhamnose- und Polyketidsynthese codieren, umfassen, insbesondere die Sequenzen gemäß SEQ ID NOS: 1, 2, 3 und 51.

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Alle zur Spinosyn-Biosynthese oder zur Synthese von Vorstufen, wie sie nachstehend definiert sind, benötigten DNA-Sequenzen können sich somit auf einem einzelnen Vektor befinden. Diese Nucleinsäuren können aber auch auf zwei oder mehreren Vektoren vorliegen und gleichzeitig oder nacheinander in einer Wirtszelle exprimiert werden.

Alle ORF's der erfindungsgemäßen Nucleinsäuren können von ihren eigenen Promotoren oder von heterologen Promotoren angeschaltet werden.

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Gegenstand der vorliegenden Erfindung sind auch die regulatorischen Regionen, welche natürlicherweise, d.h. im Ursprungsorganismus *S. spinosa*, die Transkription der erfindungsgemäßen Nucleinsäuren kontrollieren.

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Der Ausdruck "regulatorische Regionen", wie er hierin verwendet wird, bezieht sich auf Promotoren, Repressor- oder Aktivator-Bindungsstellen, Repressor- oder Aktivatorsequenzen, und Terminatoren. Ferner sind genetisch mobile Elemente, welche natürlicherweise, d.h. im Ursprungsorganismus *S. spinosa* vorkommen, ebenfalls von diesem Ausdruck umfasst. Solche genetisch mobilen Elemente können transposable oder mobilisierbare Elemente oder funktionelle Teile davon, IS-Elemente oder andere Insertionselemente sein. Weiterhin sind auch amplifizierbare DNA-Elemente (Amplifiable Units of DNA, AUD; Fishman and Hershberger, 1983), welche natürlicherweise, d.h. im Ursprungsorganismus *S. spinosa* vorkommen, von diesem Ausdruck umfasst. Die Erfindung betrifft auch jede Kombination dieser regulatorischen Regionen untereinander oder mit heterologen DNA-Fragmenten, wie z.B. Promotoren, Repressor oder Aktivator-Bindungsstellen, transposablen, mobilisierbaren oder transduzierbaren Elementen.

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Gegenstand der vorliegenden Erfindung sind weiterhin DNA-Konstrukte, die zumindest eine erfindungsgemäße Nucleinsäure und einen heterologen Promotor umfassen.

Der Ausdruck "heterologer Promotor", wie er hierin verwendet wird, bezieht sich auf einen Promotor, der im Ursprungsorganismus nicht die Expression des betreffenden Gens (ORF's) kontrolliert.

5 Die Auswahl von heterologen Promotoren ist davon abhängig, ob zur Expression pro- oder eukaryotische Zellen oder zellfreie Systeme verwendet werden. Ein bevorzugtes Beispiele für einen heterologen Promotor ist der Promotor des *mel*-Gens aus dem Vektor pIJ702 (The John Innes Foundation, Norwich, UK 1985). Die heterologe Expression kann z.B. eingesetzt werden, um zu einer Steigerung der Produktion von Spinosyn im Vergleich zum natürlichen Spinosyn-Produzenten zu gelangen.

10 Gegenstand der Erfindung sind ferner Vektoren, die zumindest eine der erfindungsgemäßen Nucleinsäuren enthalten. Als Vektoren können alle in 15 molekularbiologischen Laboratorien verwendeten Phagen, Plasmide, Phagmide, Phasmide, Cosmide, YACs, BACs, künstliche Chromosomen oder Partikel, die für einen Partikelbeschuss geeignet sind, verwendet werden.

20 Bevorzugte Vektoren sind solche, die geeignet sind zur Übertragung und Replikation in oder Integration ins Genom von Actinomyceten, wie z.B. Streptomyceten.

25 Besonders bevorzugt sind BAC-Vektoren, insbesondere solche BAC-Vektoren, die in der Weise modifiziert sind, dass sie zur Übertragung in Actinomyceten, wie z.B. Streptomyceten, sowie zur Replikation in, oder Integration ins Genom von Actinomyceten, wie z.B. Streptomyceten, geeignet sind.

30 BAC-Vektoren (Bacterial Artificial Chromosome) sind entwickelt worden zur Klonierung von großen DNA-Fragmenten (Shizuya et al., 1992). Es handelt sich um "single-copy" Plasmide mit einem F-Faktor Origin, die DNA-Fragmente mit einer durchschnittlichen Größe von 120 Kilobasenpaaren (kb) tragen können. Sie sind replizierbar in *Escherichia coli*. Der BAC-Vektor pBeloBAC11 (Kim et al., 1996)

trägt einen T7 und einen SP6 Promotor, welche die Klonierungsstelle flankieren und als Startbereich für Sequenzierungsprimer sowie zur Generierung von RNA-Transkripten verwendet werden können.

5 Am meisten bevorzugt sind die am 20. August 1999 bei der Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D-38124 Braunschweig, in Übereinstimmung mit den Bestimmungen des Budapester Vertrages unter den Hinterlegungsnummern DSM 13010, DSM 13011 und DSM 13012 hinterlegten BAC-Shuttleklone, die Gegenstand der vorliegenden Erfindung sind.

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Die hinterlegten BAC-Shuttleklone P11/G6, P8/G11 und P11/B10 tragen jeweils ein mindestens 100 kb großes DNA-Fragment aus *S. spinosa*. Die Klonen P11/G6 und P11/B10 tragen jeweils einen Teil der Nucleinsäuresequenz gemäß SEQ ID NO: 4, 15 sowie die angrenzenden vollständigen Nucleinsäuresequenzen gemäß SEQ ID NOS: 5 und 6, sowie einen an die Nucleotidsequenz gemäß SEQ ID NO: 6 3'-angrenzende DNA-Bereich (Abb. 7). Der Klon P8/G11 trägt einen Teil der Nucleinsäuresequenz gemäß SEQ ID NO: 6, die vollständigen Nucleinsäuresequenzen gemäß SEQ ID NOS: 5 und 4, sowie einen an die Sequenz gemäß SEQ ID NO: 4 3'-angrenzenden 20 DNA-Bereich (Abb. 7).

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Gegenstand der vorliegenden Erfindung sind auch Wirtszellen, die zumindest eine der erfindungsgemäßen Nucleinsäuren enthalten. Als Wirtszelle eignen sich sowohl prokaryotische Zellen, vorzugsweise Actinomyceten, besonders bevorzugt Streptomy- 25 ceten, als auch eukaryotische Zellen, wie Säugerzellen, Pflanzenzellen oder Hefezellen.

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In besonderer Weise können die erfindungsgemäßen Nucleinsäuren in pflanzliche Zellen übertragen und exprimiert werden. Hierdurch können transgene Pflanzen 30 hergestellt werden, die das pflanzenschützende, insektizide Spinosyn bzw. Derivate davon produzieren. Eine Übertragung der erfindungsgemäßen Nucleinsäuren in die

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Pflanzenzellen oder pflanzliche Zellkulturen kann mit üblichen Verfahren u.a. auch durch Partikelbeschuss erfolgen.

5 Gegenstand der vorliegenden Erfindung sind weiterhin die Polypeptide, die von den erfindungsgemäßen Nucleinsäuren codiert werden. Die erfindungsgemäßen Polypeptide können ein vollständiges Enzym darstellen, das einen Schritt der Spinosyn-Biosynthese katalysiert. Jedoch sind auch solche Polypeptide von der Erfindung erfasst, die nur einen Teil der vollständigen Aminosäuresequenz des betreffenden Enzyms aufweisen.

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Der Ausdruck "Teilsequenz", wie er hierin verwendet wird, bezieht sich somit auf die Aminosäuresequenz eines Polypeptids, das noch die Aktivität des entsprechenden vollständigen Enzyms oder einer enzymatisch aktiven Domäne ausüben kann.

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Im Folgenden werden bevorzugte erfindungsgemäße Nucleinsäuren und Polypeptide mit Bezug auf die entsprechenden SEQ ID NOS näher charakterisiert.

SEQ ID NOS: 7 und 8, ORF1:

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Nucleotidpositon 828 bis 1 der SEQ ID NO: 4, 275 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 9 und 10, ORF2:

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Nucleotidposition 1.283 bis 2.455 der SEQ ID NO: 4, 390 Aminosäuren;
das ableitbare Genprodukt ist eine Glycosyltransferase.

SEQ ID NOS: 11 und 12, ORF3:

Nucleotidposition 2.495 bis 3.247 der SEQ ID NO: 4, 250 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 13 und 14, ORF4:

Nucleotidposition 4.440 bis 3.253 der SEQ ID NO: 4, 395 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

5 SEQ ID NOS: 15 und 16, ORF5:

Nucleotidposition 4.578 bis 6.197 der SEQ ID NO: 4, 539 Aminosäuren;
das ableitbare Genprodukt ist ein C-C verknüpfendes Enzym, das Cyclisierungsreaktionen durchführt.

10 SEQ ID NOS: 17 und 18, ORF6:

Nucleotidposition 6.211 bis 7.404 der SEQ ID NO: 4, 397 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 19 und 20, ORF7:

15 Nucleotidposition 7.401 bis 8.300 der SEQ ID NO: 4, 299 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 21 und 22, ORF8:

20 Nucleotidposition 8.300 bis 9.466 der SEQ ID NO: 4, 388 Aminosäuren;
das ableitbare Genprodukt ist ein Enzym, das an Cyclisierungsreaktionen beteiligt ist.

SEQ ID NOS: 23 und 24, ORF9:

Nucleotidposition 10.572 bis 9.562 der SEQ ID NO: 4, 336 Aminosäuren.
das ableitbare Genprodukt ist eine 2,3-Reduktase.

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SEQ ID NOS: 25 und 26, ORF10:

Nucleotidposition 12.029 bis 10.569 der SEQ ID NO: 4, 486 Aminosäuren;
das ableitbare Genprodukt ist eine 2,3-Dehydratase.

SEQ ID NOS: 27 und 28, ORF11:

Nucleotidposition 12.549 bis 12.109 der SEQ ID NO: 4, 146 Aminosäuren; das ableitbare Genprodukt hat Homologien zu einer Thioesterase.

5 SEQ ID NOS: 29 und 30, ORF12:

Nucleotidposition 13.865 bis 12.546 der SEQ ID NO: 4, 439 Aminosäuren; das ableitbare Genprodukt ist eine Glykosyltransferase.

SEQ ID NOS: 31 und 32, ORF13:

10 Nucleotidposition 14.245 bis 15.633 der SEQ ID NO: 4, 462 Aminosäuren; das ableitbare Genprodukt ist eine 3,4-Dehydratase.

SEQ ID NOS: 33 und 34, ORF14:

15 Nucleotidposition 15.671 bis 16828 der SEQ ID NO: 4, 385 Aminosäuren; das ableitbare Genprodukt ist eine 4-Aminotransferase.

SEQ ID NOS: 35 und 36, ORF15:

Nucleotidposition 16.831 bis 17.580 der SEQ ID NO: 4, 249 Aminosäuren; das ableitbare Genprodukt ist eine N-Dimethyltransferase.

20 SEQ ID NOS: 37 und 38, ORF16:

Nucleotidposition 18.930 bis 18.205 der SEQ ID NO: 4, 241 Aminosäuren; das ableitbare Genprodukt ist eine 3,4-Reduktase.

25 SEQ ID NOS: 39 und 40, ORF17:

Nucleotidposition 19.025-19.861 der SEQ ID NO: 4, 278 Aminosäuren; das ableitbare Genprodukt ist ein Transkriptions-Regulator.

SEQ ID NOS: 41 und 42, ORF18:

Nucleotidpositionen 116-7903 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 2595:

Nucleotidpositionen 128-1402, Aminosäure Positionen 5-429 codieren eine β -

5 Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

Nucleotidpositionen 1691-2656, Aminosäurepositionen 526-847 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 2798-3052, Aminosäurepositionen 895-979 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

10 Nucleotidpositionen 3107-4372, Aminosäurepositionen 998-1419 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

Nucleotidpositionen 4688-5662, Aminosäurepositionen 1525-1849 codieren eine Acyltransferase-Domäne;

15 Nucleotidpositionen 6587-7138, Aminosäurepositionen 2158-2341 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 7409-7666, Aminosäurepositionen 2432-2517 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

SEQ ID NOS: 43 und 44, ORF19:

20 Nucleotidpositionen 7921-14379 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 2152:

Nucleotidpositionen 8029-9318, Aminosäurepositionen 37-466 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

25 Nucleotidpositionen 9634-10608, Aminosäurepositionen 572-896 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 10705-11259, Aminosäurepositionen 929-1113 codieren eine Dehydratase-Domäne;

Nucleotidpositionen 12043-13080, Aminosäurepositionen 1375-1720 codieren eine Enoylreduktase-Domäne;

30 Nucleotidpositionen 13093-13635, Aminosäurepositionen 1725-1905 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 13885-14142, Aminosäurepositionen 1989-2074 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

SEQ ID NOS: 45 und 46, ORF20:

5 Nucleotidpositionen 14424-23936 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 3170:

Nucleotidpositionen 14523-15824, Aminosäurepositionen 34-467 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

10 Nucleotidpositionen 16110-17075, Aminosäurepositionen 563-884 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 17997-18536, Aminosäurepositionen 1192-1371 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 18795-19052, Aminosäurepositionen 1458-1543 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

15 Nucleotidpositionen 19107-20387, Aminosäurepositionen 1562-1988 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

Nucleotidpositionen 20718-21692, Aminosäurepositionen 2099-2423 codieren eine Acyltransferase-Domäne;

20 Nucleotidpositionen 22620-23171, Aminosäurepositionen 2733-2916 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 23436-23693, Aminosäurepositionen 3005-3090 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

SEQ ID NOS: 47 und 48, ORF21:

25 Nucleotidpositionen 23983-38757 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 4924:

~~Nucleotidpositionen 24082-25392, Aminosäurepositionen 34-470 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;~~

30 ~~Nucleotidpositionen 25696-26661, Aminosäurepositionen 572-893 codieren eine Acyltransferase-Domäne;~~

Nucleotidpositionen 26761-27315, Aminosäurepositionen 927-1111 codieren eine Dehydratase-Domäne;

Nucleotidpositionen 28231-28782, Aminosäurepositionen 1417-1600 codieren eine Ketoreduktase-Domäne;

5 Nucleotidpositionen 29035-29265, Aminosäurepositionen 1685-1761 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

Nucleotidpositionen 29329-30624, Aminosäurepositionen 1783-2214 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

10 Nucleotidpositionen 30928-31902, Aminosäurepositionen 2316-2640 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 32827-33378, Aminosäurepositionen 2949-3132 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 33652-33900, Aminosäurepositionen 3224-3306 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

15 Nucleotidpositionen 33952-35262, Aminosäurepositionen 3324-3760 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

Nucleotidpositionen 35554-36522, Aminosäurepositionen 3858-4180 codieren eine Acyltransferase-Domäne;

20 Nucleotidpositionen 37453-37998, Aminosäurepositionen 4491-4672 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 38254-38511, Aminosäurepositionen 4758-4843 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

SEQ ID NOS: 49 und 50, ORF22:

25 Nucleotidpositionen 38808-50000 der SEQ ID NO: 5 und die Nukleotidpositionen 1 bis 5574 der SEQ ID NO: 6, Aminosäurepositionen 1 bis 5588:

~~Nucleotidpositionen 38907-40226 der SEQ ID NO: 5, Aminosäurepositionen 34-473~~
codiert eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

30 Nucleotidpositionen 40494-41453 der SEQ ID NO: 5, Aminosäurepositionen 563-882 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 41556-42119 der SEQ ID NO: 5, Aminosäurepositionen 917-1104 codieren eine Dehydratase-Domäne;

Nucleotidpositionen 43017-43568 der SEQ ID NO: 5, Aminosäurepositionen 1404-1587 codieren eine Ketoreduktase-Domäne;

5 Nucleotidpositionen 43833-44090 der SEQ ID NO: 5, Aminosäurepositionen 1676-1761 codieren eine β -Ketoacyl:Acyl-Carrier Protein Domäne;

Nucleotidpositionen 44151-45473 der SEQ ID NO: 5, Aminosäurepositionen 1782-2222 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

10 Nucleotidpositionen 45765-46730 der SEQ ID NO: 5, Aminosäurepositionen 2320-2641 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 46827-47459 der SEQ ID NO: 5, Aminosäurepositionen 2674-2884 codieren eine Dehydratase-Domäne;

Nucleotidpositionen 48378-48935 der SEQ ID NO: 5, Aminosäurepositionen 3191-3376 codieren eine Ketoreduktase-Domäne;

15 Nucleotidpositionen 49182-49412 der SEQ ID NO: 5, Aminosäurepositionen 3459-3535 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

Nucleotidpositionen 49482-50000 der SEQ ID NO: 5 und Nucleotidposition 1 bis 759 der SEQ ID NO: 6, Aminosäurepositionen 3559-3984 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

20 Nucleotidpositionen 1084-2049 der SEQ ID NO: 6, Aminosäurepositionen 4093-4414 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 2146-2697 der SEQ ID NO: 6, Aminosäurepositionen 4447-4630 codieren eine Dehydratase-Domäne;

25 Nucleotidpositionen 3604-4155 der SEQ ID NO: 6, Aminosäurepositionen 4933-5116 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 4420-4677 der SEQ ID NO: 6, Aminosäurepositionen 5205-5290 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

Nucleotidpositionen 4864-5538 der SEQ ID NO: 6, Aminosäurepositionen 5353-5577 codieren eine Thioesterase-Domäne.

SEQ ID NOS: 52 und 53, ORF23:

Nucleotidposition 344 bis 1333 der SEQ ID NO: 51, 329 Aminosäuren;
das ableitbare Genprodukt ist eine dNDP-Glucose-4,6-Dehydratase.

5 SEQ ID NOS: 54 und 55, ORF24:

Nucleotidposition 1330 bis 2247 der SEQ ID NO: 51, 305 Aminosäuren;
das ableitbare Genprodukt ist eine dNDP-4-keto-6-Deoxyglucose-3,5-Epimerase.

10 Die an der Cyclisierung des 5, 6, 5- Tricyclus beteiligten Produkte des ORF 5 (SEQ ID NO: 16) und des ORF 8 (SEQ ID NO: 22) sind aufgrund der ungewöhnlichen Cyclisierungsreaktionen von besonderem Interesse. Daher beinhaltet die vorliegende Erfindung insbesondere auch homologe Nucleinsäuren oder homologe Genprodukte. Vorzugsweise zeigen diese homologen Genprodukte mindestens eine 50 %ige, bevorzugt eine 60 %ige und besonders bevorzugt eine 70 %ige Identität auf Amino-

15 säureebene.

Weiterhin sind Antikörper Gegenstand der Erfindung, die spezifisch an die vorstehend genannten Polypeptide binden. Die Herstellung solcher Antikörper erfolgt auf die übliche Weise. Diese Antikörper können genutzt werden, um Expres-

20 sionsklone z.B. einer Genbank zu identifizieren, die die erfindungsgemäßen Nucleinsäuren tragen.

Gegenstand der vorliegenden Erfindung sind auch Verfahren zum Herstellen der erfindungsgemäßen Nucleinsäuren. Die erfindungsgemäßen Nucleinsäuren können

25 auf die übliche Weise hergestellt werden. Beispielsweise können die Nucleinsäuremoleküle vollständig chemisch synthetisiert werden. Man kann auch kurze Stücke der erfindungsgemäßen Nucleinsäuren chemisch synthetisieren und solche

Oligonucleotide radioaktiv oder mit einem Fluoreszenzfarbstoff markieren. Die markierten Oligonucleotide können auch verwendet werden, um Genbanken von

30 Organismen zu durchsuchen. Klone, an die die markierten Oligonucleotide hybridisieren, werden zur Isolierung der betreffenden DNA ausgewählt. Nach der Charak-

terisierung der isolierten DNA erhält man auf einfache Weise die erfindungsgemäßen Nucleinsäuren. Die erfindungsgemäßen Nucleinsäuren können auch mittels PCR-Verfahren unter Verwendung chemisch synthetischer Oligonucleotide hergestellt werden.

5

Gegenstand der vorliegenden Erfindung sind weiterhin Verfahren zum Herstellen der erfindungsgemäßen Polypeptide. Zur Herstellung der Polypeptide, die von den erfindungsgemäßen Nucleinsäuren codiert werden, können Wirtszellen, die zumindest eine der erfindungsgemäßen Nucleinsäuren enthalten, unter geeigneten Bedingungen kultiviert werden. Die gewünschten Polypeptide können danach auf übliche Weise aus den Zellen oder dem Kulturmedium isoliert werden. Die Polypeptide können auch in *in vitro*-Systemen hergestellt werden.

10

15

Das isolierte und charakterisierte Gencluster und benachbarte oder assoziierte DNA-Regionen stellen ein Target zur Steigerung der Spinosyn-Biosynthese durch genetische Manipulation, Über- oder Unterexpression von direkt oder indirekt an der Biosynthese involvierten Genen oder regulatorischen Sequenzen dar. Diese Manipulationen können sowohl in natürlichen Spinosyn-produzierenden Organismen als auch in gentechnisch hergestellten Spinosyn-produzierenden Organismen durchgeführt werden. Beispielsweise können ausgewählte ORF's unter die Kontrolle üblicher starker Promotoren wie dem *mel*-Promotor des Plasmides pIJ702 (John Innes Foundation, Norwich, UK, 1985) gestellt werden.

20

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Durch die Klonierung und Identifizierung der Spinosyn-Biosynthesegene schafft die vorliegende Erfindung die genetische Basis, mittels molekulargenetischer Verfahren neue Spinosyn-Vorstufen und -Derivate herzustellen.

Der Ausdruck "Spinosyn-Vorstufen", wie er hierin verwendet wird, bezieht sich auf alle nachweisbaren und alle postulierbaren Biosynthesevorstufen von Spinosyn.

30

Der Ausdruck "Spinosyn-Derivate", wie er hierin verwendet wird, bezieht sich auf Strukturderivate aller bisher bekannten Spinosyne.

5 Gegenstand der vorliegenden Erfindung ist somit auch ein Verfahren zum Herstellen von Spinosyn-Vorstufen und -Derivaten.

Die erfindungsgemäßen Nucleinsäuren können beispielsweise eingesetzt werden, um durch kombinatorische Biosynthese neue Spinosyn-Derivate mit Veränderungen des Spinosyn-Aglycons herzustellen. Dies kann z.B. dadurch erreicht werden, dass die von ORF 19 codierte, eine Acetat-Einheit einbauende Acyltransferase-Domäne ausgetauscht wird gegen eine Acyltransferase-Domäne, die eine Propionat-Einheit einbaut. In gleicher Weise kann die, eine Acetat-Einheit einbauende Acyltransferase-Domäne des ORF 18 gegen eine Acyltransferase-Domäne ausgetauscht werden, die eine Propionat-Einheit einbaut. Ferner ist es möglich beide oder jeweils eine Ketoreduktase-Domäne, die von beiden genannten ORF's codiert werden zu inaktivieren, durch eine inaktive Ketoreduktase-Domäne zu ersetzen oder zu deletieren, wodurch eine Hydroxygruppe an der entsprechenden Position im Makrocyclus biosynthetisch hergestellt werden kann. Alle Acyltransferase-, Ketoreduktase-, Dehydratase-, Enoylreduktase-, β -Ketoacyl:Acyl Carrier Protein und Thioesterase-Domänen können einzeln oder in beliebiger Kombination durch entsprechende Polyketidsynthase-Domänen mit anderer Substrat- oder Reaktionsspezifität ersetzt werden, in beliebiger Kombination miteinander fusioniert, einzeln oder in beliebiger Kombination mutagenisiert, deletiert oder dupliziert werden. Ferner können Modul-codierende Sequenzen ausgetauscht werden. So ist es denkbar die Modul 2-codierende DNA-Sequenz (Abb. 6) gegen die Modul 1- oder Modul 3, 4, 5, 6, 7, 8- oder Modul 9-codierende DNA-Sequenz (Abb. 6) zu ersetzen und funktionell zu exprimieren. Es ist auch denkbar die Modul 2-codierende DNA-Sequenz oder jede andere Modul-codierende DNA-Sequenz des Spinosyn-Polyketidsynthase-Genclusters gegen eine andere Modul-codierende DNA-Sequenz des Spinosyn-Polyketidsynthase-Genclusters, die eine andere biosynthetische Verlängerungseinheit einbaut, auszutauschen. Darüber hinaus kann jede andere Modul-codierende DNA-

Sequenz des Spinosyn-Polyketidsynthase-Genclusters gegen eine andere Modul-codierende DNA-Sequenz einer anderen Polyketidsynthase-Nukleinsäuresequenz aus *S. spinosa* oder einem anderen Organismus als *S. spinosa*, wie z.B. *Saccharopolyspora erythraea*, ausgetauscht werden.

5

Gegenstand der Erfindung sind somit auch alle Modul- oder Domänen-codierenden Nucleinsäuren, die natürlicher oder gentechnisch erzeugter Bestandteil der Spinosyn-Polyketidsynthase sind.

10

Der Ausdruck "Modul", sowie er hierin verwendet wird, bedeutet, dass eine Anordnung von drei enzymkatalytisch aktiven Domänen vorliegt, die zu eine Verlängerung der wachsenden Polyketidkette um eine biosynthetische Verlängerungseinheit führen. Bei diesen Domänen handelt es sich um eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne, eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl-Carrier Protein-Domäne. Ein Modul kann auch eine Ketoreduktase-, eine Dehydratase-, eine Enoylreduktase- und eine Thioesterase-Domäne tragen. Ein sog. Ladungsmodul, das am Beginn der Biosynthese steht kann von den genannten Domänen lediglich eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl-Carrier Protein-Domäne tragen, sowie eine enzymatisch inaktive β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne. Eine Polyketidsynthase-Domäne umfasst jeweils eine dieser genannten enzymatischen Aktivitäten.

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Die erfindungsgemäßen Nucleinsäuren können weiterhin genutzt werden, um im Zuge einer kombinatorischen Biosynthese durch Neuordnung und Expression von Spinosyn-Polyketidsynthase-Nucleinsäuresequenzen oder durch Kombination und Expression zusammen mit Polyketidsynthase-Nucleinsäuresequenzen einer anderen Polyketidsynthase codierenden Nucleinsäuresequenz aus *S. spinosa* oder einem anderen Organismus, wie z.B. *Saccharopolyspora erythraea*, Bibliotheken von rekombinanten Polyketidsynthase-Nucleinsäuresequenzen, rekombinanten Polyketidsynthase-Proteinen oder rekombinant erzeugten Polyketiden herzustellen. Diese Polyketide können durch die Verwendung der erfindungsgemäßen Nucleinsäuren

oder die Verwendung anderer Nucleinsäuren, deren ableitbaren Produkte an der Biosynthese anderer Zucker und Ankopplung ans Aglycon beteiligt sind, glycosyliert werden. Es ist bekannt, dass die Glycosylierung des Aglycons eine entscheidende Rolle bei der biologischen Aktivität am Wirkort spielt. Diese Veränderungen können sowohl in natürlichen als auch in gentechnisch hergestellten Spinosyn-produzierenden Organismen, insbesondere Bakterien, erfolgen.

Die erfindungsgemäßen Nucleinsäuren, Vektoren und regulatorischen oder genetisch mobilen Regionen können außerdem zum Auffinden von Genen verwendet werden, die für Polypeptide codieren, welche funktionell ähnliche Polyketidsynthasen oder funktionell ähnliche Produkte, die an einer Zuckerbiosynthese beteiligt sind, codieren.

Da die erfindungsgemäßen Nucleinsäuren einen umfangreichen Teil des Genoms von *S. spinosa* ausmacht, können die erfindungsgemäßen Nucleinsäuren als Marker bei der Sequenzierung des Genoms von *S. spinosa* eingesetzt werden, wodurch die Anordnung von Teilsequenzen eines Genomsequenzierungsprojektes erheblich erleichtert wird.

Somit liefern die erfindungsgemäßen Nucleinsäuren Daten, die im Rahmen eines Genomsequenzierungsprojektes und eines sich darauf aufbauenden Metabolic Engineering zur Steigerung der Spinosynproduktion eingesetzt werden können.

Erläuterungen zu den Abbildungen:

Abbildung 1: Modell für die Biosynthese der Spinosyn-Zucker D-Forosamin und 2, 3, 4-Tri-O-Methyl-L-Rhamnose.

Abbildung 2: Lage, der an der Spinosyn-Biosynthese direkt oder indirekt beteiligten DNA-Regionen 1 (SEQ ID NO: 4) und DNA-Region 2 (SEQ ID NOS: 5 und 6). Die schwarzen Balken im unteren Teil der Abbildung geben schematisch die Positionen

der Cosmid-DNA Inserts zueinander und in Bezug zu den DNA-Regionen 1 und 2 an. Die dargestellten Cosmid-Inserts wurden zur Sequenzierung der SEQ ID NOS: 1 bis 3 herangezogen.

5 Abbildung 3: Schematische Darstellung der Lage der Insert-DNA (schwarze Balken im unteren Teil der Abbildung) der benannten Cosmide, die zur Ankopplung eines Forosamin-Restes oder eines Trimethyl-Rhamnose-Restes durch Biotransformation des Spinosyn-Aglycons und Spinosyn-Pseudoaglycons herangezogen worden sind.

10 Abbildung 4: Schematische Darstellung der offenen Leserahmen (ORF's) der DNA-Region 3, die der SEQ ID NO: 51 entspricht, auf Cosmid 16-2-2.

15 Abbildung 5: Schematische Darstellung offener Leserahmen (ORF's) der DNA-Regionen 1 und 2. Die ORF's sind nummeriert von 1 bis 22 entsprechend SEQ ID NOS: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47 und 49.

20 Abbildung 6: Schematische Darstellung offener Leserahmen (ORF's) der DNA-Region 2 (SEQ ID NOS: 5 und 6) und ableitbarer Module und Domänen. SM, Startmodul; M1 bis M10, Modul 1 bis Modul 10; KS, β -Ketoacyl:Acyl Carrier Protein Synthase; AT, Acyltransferase; ACP, β -Ketoacyl:Acyl Carrier Protein; KR, Ketoreduktase; DH, Dehydratase; ER, Enoylreduktase.

25 Abbildung 7: Schematische Darstellung der Lage von BAC-Shuttleklon Insert-DNA als schwarze Balken im unteren Teil der Abbildung. Die Größe der Insert-DNA beträgt mindestens 100 kb. Durchgezogene Balken: DNA-Sequenz ist identisch mit ~~Teilen bzw. der Gesamtheit der DNA-Regionen 1 und 2.~~ Gestrichelte Balken: DNA-Sequenz liegt außerhalb des sequenzierten Bereichs.

Beispiele

Bakterienstämme und Plasmide

5 *Escherichia coli* XL1-Blue MRF' und die Cosmidvektoren SuperCos1 (Stratagene, Europe) und pOJ446 (Biermann et al., 1992) wurden verwendet zur Erstellung von Genbanken von *S. spinosa* ATCC49460 (American Type Culture Collection, U.S.A., EP-A 0 375 316). *E. coli* JM110 (Stratagene, Europe) wurde verwendet zur Propagierung von Plasmiden, die durch Transformation nach *Streptomyces* übertragen wurden. *Streptomyces albus* J1074 (Chater and Wilde, 1980; John Innes Institut in
10 Norwich, UK) wurde zur heterologen Expression von und zur Biotransformation mit Spinosyn-Biosynthesegenen eingesetzt.

Plasmid pBeloBAC11 (Kim et al., 1996) und pOJ446 (Biermann et al., 1992) wurden
15 verwendet zur Herstellung eines *E. coli* – *Streptomyces* BAC-Shuttlevektors.

Molekularbiologische Methoden

20 Molekularbiologische Methoden wie DNA-Restriktion, Agarose-Gelelektrophorese von DNA, Ligation von Restriktionsfragmenten, Kultivierung und Transformation von *E. coli* wurden durchgeführt wie beschrieben in Sambrook et. al (1989). Plasmide wurden mit Qiagen Plasmid Kit (Qiagen, Hilden, Deutschland) isoliert. Die verwendeten Enzyme stammten von Roche Diagnostics GmbH (Mannheim, Deutschland).

25 Anzucht Bedingungen and molekulargenetische Methoden mit *S. spinosa* und Streptomyceten sind beschrieben in (Hopwood et al., 1985). Alle Anzuchten in Flüssigkultur von *S. spinosa* oder Streptomyceten erfolgten aerob in Erlenmeyerkolben bei 28°C.

Die DNA-DNA-Hybridisierungen erfolgten unter Verwendung des DIG-High Prime DNA Labeling and Detection Kit nach Angaben des Herstellers (Roche Diagnostics GmbH, Mannheim, Deutschland).

5 Wachstumsmedien:

LB Sambrook et. al., 1989

10 TS Difco Bestell-Nummer 0 370-17-3 (Difco Detroit, MI, USA)

R5A Illing et al., 1985

Herstellung einer Cosmid Genbank von *S. spinosa*

15 Um eine Genbank von *S. spinosa* zu erhalten, wurde chromosomale DNA von *S. spinosa* ATCC49460 mit *Mbo*I partiell geschnitten und durch Zentrifugation im Glucosedichtegradienten aufgetrennt. Die Cosmid-DNA (SuperCos1, Stratagene Europe) wurde nach Angaben des Herstellers vorbereitet, mit den *S. spinosa* DNA-Fragmenten zwischen 35 und 45 kb ligiert und mit Hilfe des Gigapack-Verpackungssystem (Stratagene Europe) in Phagenpartikel verpackt. Die Transfektion erfolgte in *E. coli* XL-1 blue MRF'. Diese Methode wurde ebenfalls dazu verwendet
20 eine zweite *S. spinosa* Genbank anzulegen unter Verwendung des *E. coli*-*Streptomyces* Shuttle-Cosmids pOJ446.

25 Sequenzierung des Spinosynbiosynthese-Genclusters und eines DNA-Fragmentes das außerhalb dieses Clusters liegt, dessen Produkte aber an der Biosynthese von Spinosyn beteiligt sind

30 Die Insert-DNA der SuperCos1 Cosmide 16-1-8, 16-59-1, und 16-59-8 wurden sequenziert. Eine ca. 4 kb große Lücke zwischen den Cosmiden 16-59-1 und 16-1-8

wurde durch primer walking Sequenzierung eines entsprechenden Teilbereiches von Cosmid 16-59-6 geschlossen.

Eine ca. 2,3 kb große DNA-Sequenz auf dem SuperCos1 Cosmid 16-2-2 wurde sequenziert.

Identifizierung und Charakterisierung von chromosomalen DNA-Fragmenten einer BAC-Shuttlevektor-Genbank aus *S. spinosa*, die Spinosyn-Biosynthesegensequenzen tragen

Zur Herstellung des BAC-Shuttlevektors, der nicht nur in *E. coli* sondern auch in Actinomyceten wie *Streptomyces* übertragen und vermehrt werden kann, wurde der Vektor pBeloBAC11 mit *Xho*I linearisiert, und durch die Anwendung von Klenow Polymerase wurden glatte DNA-Enden hergestellt. Ein ca. 6 kb großes *Dra*I – *Eco*RV DNA-Fragment des Cosmidvektors pOJ446, das den Replikationsursprung des Plasmides SCP2*, das Apramycinresistenzgen sowie den *oriT* zum konjugativen Transfer trägt, wurde mit dem linearisierten BAC-Vektor ligiert. Der resultierende Vektor erhielt die Bezeichnung pEBZ333.

Ausgehend von partiell mit *Mbo*I geschnittener genomischer DNA des Stammes *S. spinosa* ATCC49460 und dem mit *Bam*HI geschnittenen Vektor pEBZ333 wurde eine BAC-Genbank erstellt.

Analyse und Annotation offener Leserahmen direkt oder indirekt an der Spinosyn-Biosynthese beteiligter DNA-Sequenzen

~~Ausgehend von der Sequenz gemäß SEQ ID NOS: 1 bis 3 wurden offene Leserahmen (ORF's) identifiziert, die direkt oder indirekt an der Biosynthese von Spinosyn beteiligt sind. Diese ORF's wurden in zwei DNA-Regionen unterteilt, die als DNA-Region 1 und DNA-Region 2 (Abb. 2 und 5) bezeichnet werden und die~~

Sequenzen gemäß SEQ ID NO: 4 bzw. 5 und 6 tragen. Die DNA-Region 1 trägt offene Leserahmen, deren Produkte an der Modifizierung und Tricyclusbildung des Spinosyn-Aglycons beteiligt sind, während die DNA-Region 2 (Abb. 2, 5 und 6) offene Leserahmen umfasst, deren Produkte die Spinosyn-Polyketidsynthase codieren. Die beiden jeweils ersten Nucleotide dieser DNA-Regionen liegen unmittelbar nebeneinander (Abb. 2, 3 und 5).

Eine weitere DNA-Region 3 (SEQ ID NO: 51) liegt außerhalb dieses Clusters von DNA-Sequenzen und trägt offene Leserahmen, deren Produkte ebenfalls an der Biosynthese des Spinosyn-Zuckers Trimethyl-Rhamnose beteiligt sind.

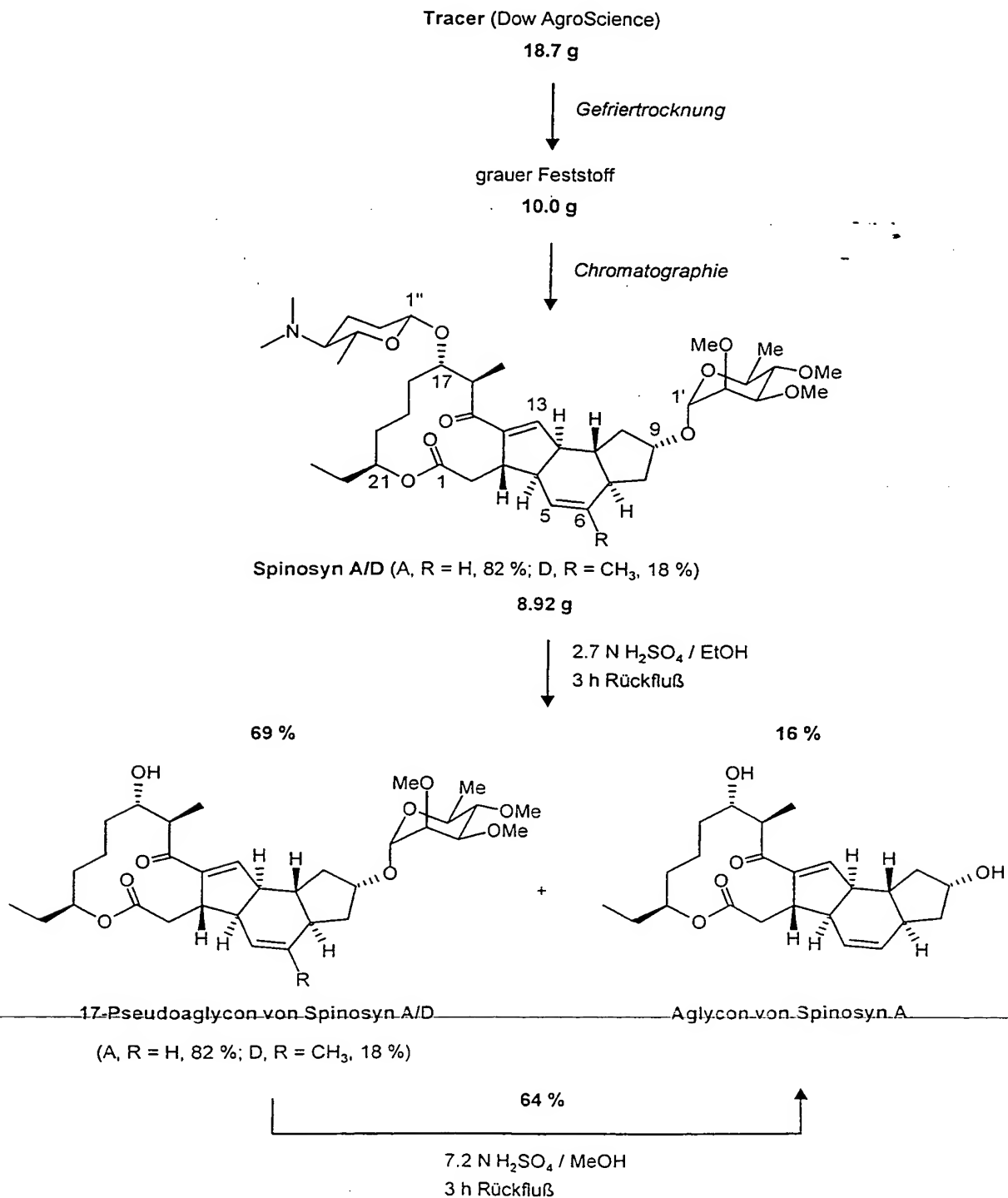
Herstellung des Spinosyn-Aglycons und 17-Pseudoaglycons aus Tracer®

Ausgehend von 18.7 g des kommerziell erhältlichen Produktes Tracer® wurden nach Gefriertrocknung und Säulenchromatographie an Kieselgel 8.92 g Spinosyn A und D in einem Verhältnis von 82:18 gewonnen.

Die Hydrolyse des Aminozuckers Forosamin gelang mit 2.7 N Schwefelsäure in Ethanol unter Rückfluß. Dabei fiel der Großteil des entstehenden 17-Pseudoaglycons von Spinosyn A/D aus. Im Filtrat wurden neben weiterem 17-Pseudoaglycon in Abhängigkeit von der Reaktionsdauer geringe bis mittlere Mengen des Spinosyn-Aglycons gefunden.

Eine vollständige Hydrolyse zum Aglycon gelang unter etwas drastischeren Bedingungen (7.2 N Schwefelsäure in Methanol unter Rückfluß). Die Aglycon-Fraktion enthielt ausschließlich Aglycon von Spinosyn A. Dies stimmt sehr gut mit der Literatur überein (Creemer et al., 1998), die unter entsprechenden Reaktionsbedingungen eine vollständige Zersetzung des Pseudoaglycons von Spinosyn D beschreibt. Als Ursache nehmen die Autoren eine leichtere Protonierung der 5,6-Doppelbindung bei Spinosyn D unter Bildung eines tertiären Carbokations und anschließende Umlagerungen an.

Es konnten somit ausgehend von 18.7 g käuflichem Tracer® 3.0 g Aglycon von Spinosyn A hergestellt werden.



Gewinnung von Spinosyn A/D aus Tracer®

Die Gefriertrocknung von 18,7 g Tracer® lieferten 10,0 g grauen Feststoff. Nach Säulenchromatographie dieses Feststoffes an 800 cm³ Kieselgel (Eluent: Dichlormethan/Methanol 95:5) erhielt man 8,92 g reines Spinosyn A/D (82 % A, 18 % D). – DC: R_f (SiO₂, Dichlormethan/Methanol 9:1) = 0,46. – ¹H-NMR: CDCl₃, δ = 6,77 (s, 13-H); 5,88 (d, 5-H von Spinosyn A); 5,80 (m, 6-H von Spinosyn A); 5,49 (m, 5-H von Spinosyn D); 4,87 (d, 1'-H); 4,67 (m, 21-H); 4,43 (d, 1''-H); 4,31 (m, 9-H) u. a. – LC/MS: Elektrospray Positiv; Peak bei RT 44,0 min: m/z = 733 (100 %) [M+H]⁺ (Spinosyn A); Peak bei 44,7 min: m/z = 747 (100 %) [M+H]⁺ (Spinosyn D).

Darstellung des 17-Pseudoaglycons von Spinosyn A/D:

8,65 g (11,81 mmol) Spinosyn A/D wurden in 61 ml Ethanol gelöst und mit 104 ml Wasser und 208 ml 4 N H₂SO₄ versetzt. Nach 3 h Erwärmen unter Rückfluß wurde der ausgefallene Feststoff (A) abfiltriert und getrennt vom Filtrat (B) aufgearbeitet. Der Feststoff (A) wurde mit 1 N H₂SO₄ gewaschen, in 140 ml Dichlormethan aufgenommen, nacheinander mit gesätt. NaHCO₃-Lösung und gesätt. NaCl-Lösung gewaschen, über Na₂SO₄ getrocknet und im Vakuum eingeeengt. Umkristallisation aus Ethanol lieferten 3,03 g 17-Pseudoaglycon von Spinosyn A/D und Mutterlauge (C). Das Filtrat (B) wurde mehrmals mit Dichlormethan extrahiert. Die Extrakte wurden nacheinander mit gesätt. NaHCO₃-Lösung und gesätt. NaCl-Lösung gewaschen, über Na₂SO₄ getrocknet und im Vakuum eingeeengt. Der Rückstand wurde vereint mit der im Vakuum eingeeengten Mutterlauge (C) und durch Säulenchromatographie an 650 cm³ Kieselgel (Eluent: Cyclohexan/Essigsäureethylester 1:1, dann 100 % Essigsäureethylester) aufgetrennt. Man erhielt neben weiteren 1,76 g 17-Pseudoaglycon von Spinosyn A/D 0,78 g (16 %) Aglycon von Spinosyn A. Die Gesamtausbeute von 17-Pseudoaglycon von Spinosyn A/D betrug 4,79 g (69 %). – a) 17-Pseudoaglycon von Spinosyn A/D (82 % A, 18 % D): DC: R_f (SiO₂, Essigsäureethylester) = 0,48. – ¹H-NMR: CDCl₃, δ = 6,78 (s, 13-H); 5,88 (d, 5-H von Spinosyn A); 5,80 (m, 6-H von Spinosyn A); 5,49 (m, 5-H von Spinosyn D); 4,86 (d,

1'-H); 4,70 (m, 21-H); 4,32 (m, 9-H) u. a. - LC/MS: Elektrospray Positiv; Peak bei RT 40,7 min: $m/z = 609$ (100 %) $[M+NH_4]^+$, $m/z = 641$ (10 %) $[M+NH_4+CH_3OH]^+$ (Pseudoaglycon von Spinosyn A); Peak bei RT 41,4 min: $m/z = 623$ (100 %) $[M+NH_4]^+$, $m/z = 655$ (8 %) $[M+NH_4+CH_3OH]^+$ (Pseudoaglycon von Spinosyn D). –
 5 b) Aglycon von Spinosyn A: DC: R_f (SiO₂, Essigsäureethylester) = 0,29. – ¹H-NMR: CDCl₃, $\delta = 6,80$ (s, 13-H); 5,89 (d, 5-H); 5,80 (m, 6-H); 4,70 (m, 21-H); 4,44 (m, 9-H) u. a. - LC/MS: Elektrospray Positiv; Peak bei RT 36,8 min: $m/z = 420$ (100 %) $[M+NH_4]^+$, $m/z = 452$ (10 %) $[M+NH_4+CH_3OH]^+$.

10 Darstellung des Aglycon von Spinosyn A/D

4,30 g (7,29 mmol) Pseudoaglycon von Spinosyn A/D wurden in 190 ml Methanol gelöst und mit 285 ml 7,2 N H₂SO₄ versetzt. Nach 3 h Erwärmen unter Rückfluß wurde die abgekühlte Reaktionsmischung vorsichtig in 1700 ml gesättigte NaHCO₃-
 15 Lösung gegeben. Man extrahierte mit Diethylether, wusch die Extrakte nacheinander mit gesätt. NaHCO₃-Lösung und gesätt. NaCl-Lösung, trocknete über Na₂SO₄ und engte im Vakuum ein. Nach Säulenchromatographie dieses Feststoffes an 650 cm³ Kieselgel (Eluent: Cyclohexan/Essigsäureethylester 1:2, dann 100 % Essigsäureethylester) erhielt man 1,88 g (64 %) Aglycon von Spinosyn A. – DC: R_f (SiO₂, Essigsäureethylester) = 0,29. – ¹H-NMR: CDCl₃, $\delta = 6,80$ (s, 13-H); 5,89 (d, 5-H); 5,80 (m, 6-H); 4,70 (m, 21-H); 4,44 (m, 9-H) u. a. – LC/MS: Elektrospray Positiv; Peak bei RT 36,6 min: $m/z = 420$ (100 %) $[M+NH_4]^+$, $m/z = 452$ (14 %) $[M+NH_4+CH_3OH]^+$ (Aglycon von Spinosyn A).
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25 Forosaminylierung des Spinosyn-Aglycons und Anknüpfung eines Trimethyl-Rhamnosezuckers an das Spinosyn-Aglycon durch Biotransformation mit einem rekombinanten *Streptomyces* Stamm, der Spinosyn-Zuckerbiosynthesegene heterolog exprimiert

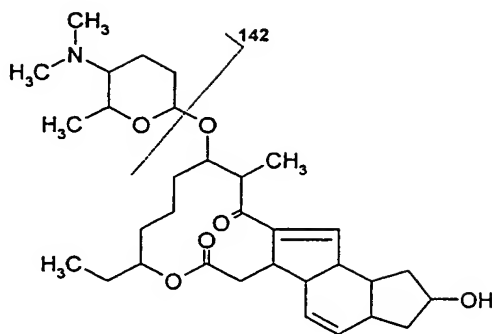
30 20 ml R5A Medium (Illing et al., 1989) mit 5 µg Apramycin / ml wurde mit Mycel des rekombinanten Stammes *S. albus* (165-1) oder *S. albus* (165-8) angeimpft und

24 h aerob bei 28°C bebrütet. Diese Kultur wurde mit 50 µg/ml des hergestellten Spinosyn-Aglycons (100 µl einer 1 %igen Stammlösung in Methanol; Herstellung siehe Kapitel "Herstellung des Spinosyn-Aglycons und 17-Pseudoaglycons aus Tracer[®]", „Gewinnung von Spinosyn A/D aus Tracer[®]" und „Darstellung des Aglycon von Spinosyn A/D“) versetzt und ca. 120 h bei 28°C aerob inkubiert. Als Kontrolle wurde in gleicher Weise *S. albus* (pEBZ340; pOJ446-Vektor mit einem ca. 1,8 kb großen Spinosyn-PKS tragenden DNA-Fragment aus Cosmid 16-1-8) kultiviert und mit Spinosyn-Aglycon versetzt. Die Kulturen wurden nach Inkubation zur Abtrennung von Zellmycel zentrifugiert und der Überstand (20 ml) wurde mit 25 ml Methanol versetzt.

Je 35 ml des mit Methanol versetzten Kulturüberstandes wurden lyophilisiert, mit 15 ml Wasser aufgenommen und zweimal mit je 10 ml Essigsäureethylester extrahiert. Die vereinten organischen Phasen wurden zur Trockene eingengt und mit 350 µl Methanol aufgenommen. Ein Aliquot dieser Extrakte wurde mittels LC/MS mit Elektrospray Positiv-Ionisation untersucht.

Der Kulturüberstand der Anzucht von *S. albus* (165-1) enthielt eine Verbindung mit dem Molekulargewicht eines forosaminylierten Aglycons von Spinosyn A sowie Spinosyn A.

Peak 1: RT = 41,0 min: m/z = 544 (100 %) [M+H]⁺, m/z = 576 (20 %) [M+H+CH₃OH]⁺ (Forosaminyliertes Aglycon von Spinosyn A); LC/MS/MS: m/z = 142 (30 %) (Forosamin-Fragment).



Forosaminyliertes Aglycon von Spinosyn A
Molekulargewicht = 543
Summenformel = $C_{32}H_{49}NO_6$

Peak 2: RT = 44,2 min: $m/z = 733$ (100 %) $[M+H]^+$ (Spinosyn A); LC/MS/MS: $m/z = 142$ (21 %) (Forosamin-Fragment).

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Der Kulturüberstand von *S. albus* (165-8) enthielt eine Verbindung mit dem Molekulargewicht eines Forosaminylierten Aglycons von Spinosyn A.

Peak 1: RT = 40,9 min: $m/z = 544$ (100 %) $[M+H]^+$, $m/z = 576$ (20 %) $[M+H+CH_3OH]^+$ (Forosaminyliertes Aglycon von Spinosyn A); LC/MS/MS: $m/z = 142$ (39 %) (Forosamin-Fragment).

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Der Kulturüberstand von *S. albus* (pEBZ340) enthielt keine Verbindungen mit MW 544 und kein Spinosyn A.

Forosaminylierung des Spinosyn-17-Pseudoaglycons durch Biotransformation mit einem rekombinanten *Streptomyces* Stamm, der Spinosyn Zuckerbiosynthesegene heterolog exprimiert

20 ml R5A Medium (Illing et al., 1989) mit 5 μ g Apramycin / ml wurde mit Mycel des rekombinanten Stammes *S. albus* (165-1) oder *S. albus* (165-8) angeimpft und 24 h aerob bei 28°C bebrütet. Diese Kultur wurde mit 50 μ g/ml des hergestellten 17-Pseudoaglycons von Spinosyn (100 μ l einer 1 %igen Stammlösung in Methanol; Herstellung siehe Kapitel "Herstellung des Spinosyn-Aglycons und 17-Pseudo-

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aglycons aus Tracer[®], „Gewinnung von Spinosyn A/D aus Tracer[®]“ und „Darstellung des 17-Pseudoaglycon von Spinosyn A/D““) versetzt und ca. 120 h bei 28°C aerob inkubiert. Die Kulturen wurden nach Inkubation zur Abtrennung von Zellmycel zentrifugiert und der Überstand (20 ml) wurde mit 25 ml Methanol versetzt.

Je 35 ml des mit Methanol versetzten Kulturüberstandes wurden lyophilisiert, mit 15 ml Wasser aufgenommen und zweimal mit je 10 ml Essigsäureethylester extrahiert. Die vereinten organischen Phasen wurden zur Trockene eingedunstet und mit 350 µl Methanol aufgenommen. Ein Aliquot dieser Extrakte wurde mittels LC/MS mit Elektrospray Positiv-Ionisation untersucht.

Der Kulturüberstand von *S. albus* (165-1) enthielt Spuren von Spinosyn A und D.

Peak 1: RT = 44,2 min: m/z = 733 (100 %) [M+H]⁺ (Spinosyn A); LC/MS/MS: m/z = 142 (8 %) (Forsamin-Fragment).

Peak 2: RT = 44,7 min: m/z = 747 (100 %) [M+H]⁺ (Spinosyn D); LC/MS/MS: m/z = 142 (37 %) (Forsamin-Fragment).

Der Kulturüberstand von *S. albus* (165-8) enthielt Spuren von Spinosyn A und D.

Peak 1: RT = 44,1 min: m/z = 733 (100 %) [M+H]⁺ (Spinosyn A).

Peak 2: RT = 44,7 min: m/z = 747 (100 %) [M+H]⁺ (Spinosyn D).

Hinterlegung von Mikroorganismen

Folgende Mikroorganismen und Plasmide sind bei der Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D- 38124 Braunschweig, in Übereinstimmung mit den Bestimmungen des Budapester Vertrages hinterlegt worden.

Mikroorganismus und Plasmid

Hinterlegungsnummer

	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-1-8	DSM 12961
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-2-2	DSM 12962
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-59-1	DSM 12963
5	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-59-6	DSM 12964
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-59-8	DSM 12965
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 165-1	DSM 13005
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 165-8	DSM 13007
	<i>E. coli</i> DH10B mit dem BAC Shuttle-Klon P8 / G11	DSM 13012
10	<i>E. coli</i> DH10B mit dem BAC Shuttle-Klon P11 / B10	DSM 13011
	<i>E. coli</i> DH10B mit dem BAC Shuttle-Klon P11 / G6	DSM 13010

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Patentansprüche

- 5
1. Nucleinsäure, welche zumindest eine Region umfasst, die für eine Enzymaktivität codiert, welche an der Biosynthese von Spinosynen beteiligt ist.
 2. Nucleinsäure gemäß Anspruch 1, dadurch gekennzeichnet, dass es sich um einzelsträngige oder doppelsträngige DNA oder RNA handelt.
 - 10 3. Nucleinsäure gemäß Anspruch 2, dadurch gekennzeichnet, dass es sich um ein DNA-Fragment handelt.
 4. Nucleinsäure gemäß Anspruch 3, dadurch gekennzeichnet, dass sie alle Regionen umfasst, die für Enzymaktivitäten codieren, welche an der Biosynthese von Spinosynen beteiligt sind.

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 5. Nucleinsäure gemäß einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass es sich um Enzymaktivitäten von Polyketidsynthasen, Methyltransferasen, Glycosyltransferasen, Epimerasen, Aminotransferasen, Dimethyltransferasen, Reduktasen, Dehydratasen und/oder Cyclisierungsenzymen handelt.

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 6. Nucleinsäure gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass sie aus *Saccharopolyspora spinosa* stammt.

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 7. Nucleinsäure gemäß Anspruch 1, umfassend zumindest eine Sequenz ausgewählt aus

-
- (a) den Sequenzen gemäß SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 52 oder 54,
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- (b) zumindest 14 Basenpaare langen Teilsequenzen der unter (a) definierten Sequenzen,
 - (c) Sequenzen, welche an die unter (a) definierten Sequenzen hybridisieren
 - (d) Sequenzen, welche eine zumindest 70 %ige Identität zu den unter (a) definierten Sequenzen aufweisen,
 - (e) Sequenzen, welche zu den unter (a) definierten Sequenzen-komplementär sind, und
 - (g) Sequenzen, welche aufgrund der Degeneriertheit des genetischen Codes für dieselbe Aminosäuresequenz kodieren wie die unter (a) bis (d) definierten Sequenzen.
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8. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie die Sequenz gemäß SEQ ID NOS: 1 bis 6 umfasst.
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9. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie die Sequenz gemäß SEQ ID NO: 4 umfasst.
10. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie die Sequenz gemäß SEQ ID NOS: 5 und 6 umfasst.
- 25
11. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie zumindest eine Sequenz gemäß SEQ ID NOS: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37 oder 39 umfasst.
- 30
12. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie zumindest eine Sequenz gemäß SEQ ID NOS: 41, 43, 45, 47 oder 49 umfasst.

13. Regulatorische Region, welche die Transkription einer Nukleinsäure gemäß einem der Ansprüche 1 bis 7 in *Saccharopolyspora spinosa* kontrolliert.
- 5 14. DNA-Konstrukt umfassend eine Nucleinsäure gemäß einem der Ansprüche 1 bis 12 und zumindest einen heterologen Promotor.
- 10 15. Vektor umfassend zumindest eine Nucleinsäure gemäß einem der Ansprüche 1 bis 12, eine regulatorische Region gemäß Anspruch 13 oder ein DNA-Konstrukt gemäß Anspruch 14.
- 15 16. Vektor gemäß Anspruch 15, dadurch gekennzeichnet, dass die Nucleinsäure funktionell mit regulatorischen Sequenzen verknüpft ist, welche die Expression der codierenden Regionen der Nucleinsäure in pro- oder eukaryotischen Zellen gewährleisten.
- 20 17. Vektor gemäß Anspruch 15 oder 16, dadurch gekennzeichnet, dass es sich um einen BAC-Vektor handelt.
- 25 18. Vektor gemäß Anspruch 17, dadurch gekennzeichnet, dass es sich um einen Vektor handelt, der den BAC-Klonen mit den Hinterlegungsnummern DSM 13010, DSM 13011 oder 13012 entspricht.
19. Wirtszelle enthaltend eine Nucleinsäure gemäß einem der Ansprüche 1 bis 12, eine regulatorische Region gemäß Anspruch 13, ein DNA-Konstrukt gemäß Anspruch 14 oder einen Vektor gemäß einem der Ansprüche 15 bis 18.
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20. Wirtszelle gemäß Anspruch 19, dadurch gekennzeichnet, dass es sich um eine pro- oder eukaryotische Zelle handelt.

21. Wirtszelle gemäß Anspruch 20, dadurch gekennzeichnet, dass die prokaryotische Zelle zur Gruppe der Actinomyceten, bevorzugt zur Gruppe der Streptomyceten gehört.
- 5 22. Wirtszelle gemäß Anspruch 20, dadurch gekennzeichnet, dass die eukaryotische Zelle eine Pflanzenzelle ist.
23. Polypeptid, welches von einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 codiert wird.
- 10 24. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer Methyltransferase aufweist.
- 15 25. Polypeptid gemäß Anspruch 24, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NOS: 8, 12, 14, 18 oder 20, oder eine Teilsequenz davon aufweist.
- 20 26. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer Glycosyltransferase aufweist.
27. Polypeptid gemäß Anspruch 26, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NOS: 10 oder 30, oder eine Teilsequenz davon aufweist.
- 25 28. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität eines C-C verknüpfenden Enzyms, das Cyclisierungsreaktionen durchführt, aufweist.
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- 30 29. Polypeptid gemäß Anspruch 28, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 16 oder eine Teilsequenz davon aufweist.

30. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität eines Enzyms, das an Cyclisierungsreaktionen beteiligt ist, aufweist.

5 31. Polypeptid gemäß Anspruch 30, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 22 oder eine Teilsequenz davon aufweist.

32. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer 2,3-Reduktase aufweist.

10 33. Polypeptid gemäß Anspruch 32, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 24 oder eine Teilsequenz davon aufweist.

34. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer 2,3-Dehydratase aufweist.

15 35. Polypeptid gemäß Anspruch 34, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 26 oder eine Teilsequenz davon aufweist.

20 36. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer Thioesterase aufweist.

37. Polypeptid gemäß Anspruch 36, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 28 oder eine Teilsequenz davon aufweist.

25 38. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer 3,4-Dehydratase aufweist.

39. Polypeptid gemäß Anspruch 38, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 32 oder eine Teilsequenz davon aufweist.

40. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer 4-Aminotransferase aufweist.
- 5 41. Polypeptid gemäß Anspruch 40, dadurch gekennzeichnet, dass es die AmiNO:säuresequenz gemäß SEQ ID no: 34 oder eine Teilsequenz davon aufweist.
- 10 42. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer N-Dimethyltransferase aufweist.
43. Polypeptid gemäß Anspruch 42, dadurch gekennzeichnet, dass es die AmiNO:säuresequenz gemäß SEQ ID NO: 36 oder eine Teilsequenz davon aufweist.
- 15 44. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer 3,4-Reduktase aufweist.
- 20 45. Polypeptid gemäß Anspruch 44, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 38 oder eine Teilsequenz davon aufweist.
- 25 46. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität eines Transkriptions-Regulators aufweist.
47. Polypeptid gemäß Anspruch 46, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 40 oder eine Teilsequenz davon aufweist.
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- 30 48. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer Polyketidsynthase aufweist.

49. Polypeptid gemäß Anspruch 48, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NOS: 42, 44, 46, 48 oder 50, oder eine Teilsequenz davon aufweist.
50. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer Glucose-Dehydratase aufweist.
51. Polypeptid gemäß Anspruch 50, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 53 aufweist.
52. Polypeptid gemäß Anspruch 23, dadurch gekennzeichnet, dass es die Aktivität einer 3,5-Epimerase aufweist.
53. Polypeptid gemäß Anspruch 52, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 55 aufweist.
54. Enzyme, die an Cyclisierungsreaktionen beteiligt sind, dadurch gekennzeichnet, dass sie die Aminosäuresequenz gemäß SEQ ID NO: 15 oder 22, oder eine Teilsequenz davon, welche zumindest noch eine Teilreaktion durchführen kann, umfassen oder eine mindestens 50 %ige Identität dazu auf Aminosäureebene aufweisen.
55. Antikörper, welcher spezifisch mit einem Polypeptid gemäß einem der Ansprüche 23 bis 54 reagiert.
56. Verfahren zur Herstellung einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7, umfassend die folgenden Schritte:

- (a) Vollständige chemische Synthese auf an sich bekannte Weise oder

5 (b) chemische Synthese von Oligonucleotiden, Markieren der Oligonucleotide, Hybridisieren der Oligonucleotide an DNA einer genomischen oder cDNA-Bank, die ausgehend von genomischer DNA bzw. mRNA aus *Saccharopolyspora spinosa* hergestellt wurde, Selektieren von positiven Klonen und Isolieren der hybridisierenden DNA aus positiven Klonen oder

(c) chemische Synthese von Oligonucleotiden und Amplifizierung der Ziel-DNA mittels PCR.

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57. Verfahren zur Herstellung eines Polypeptids gemäß einem der Ansprüche 23 bis 54, umfassend

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(a) das Kultivieren einer Wirtszelle gemäß einem der Ansprüche 19 bis 22 unter Bedingungen, die die Expression der Nucleinsäure gemäß einem der Ansprüche 1 bis 7 gewährleisten, oder

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(a1) das Exprimieren einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 in einem *in vitro*-System, und

(b) das Gewinnen des Polypeptids aus der Zelle, dem Kulturmedium oder dem *in vitro*-System.

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58. Verfahren zum Herstellen von Spinosyn-Derivaten, einschließlich Spinosyn-Vorstufen, umfassend die folgenden Schritte:

(a) Austauschen zumindest einer Modul-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Modul-codierende Nucleinsäuresequenz gemäß Anspruch 7, oder

30

- (b) Austauschen zumindest einer Modul-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Modul-codierende Nucleinsäuresequenz aus *S. spinosa*, oder
- 5 (c) Austauschen zumindest einer Modul-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Modul-codierende Nucleinsäuresequenz aus einem anderen Organismus als *S. spinosa*, oder
- 10 (d) Austauschen zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Domänen-codierende Nucleinsäuresequenz gemäß Anspruch 7, oder
- 15 (e) Austauschen zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Domänen-codierende Nucleinsäuresequenz aus *S. spinosa*, oder
- 20 (f) Austauschen zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Domänen-codierende Nucleinsäuresequenz aus einem anderen Organismus als *S. spinosa*, oder
- 25 (g) Austauschen einer ersten Acyltransferase-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen eine zweite Acyltransferase-codierende Nucleinsäuresequenz gemäß Anspruch 7, wobei die zweite Acyltransferase eine unterschiedliche Substratspezifität aufweist als die erste Acyltransferase, oder
-
- 30 (h) Austauschen einer ersten Acyltransferase-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen eine zweite Acyltransferase-codierende Nucleinsäuresequenz aus *S. spinosa*, wobei die zweite

Acyltransferase eine unterschiedliche Substratspezifität aufweist als die erste Acyltransferase, oder

5

- (i) Austauschen einer ersten Acyltransferase-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen eine zweite Acyltransferase-codierende Nucleinsäuresequenz aus einem anderen Organismus als *S. spinosa*, wobei die zweite Acyltransferase eine unterschiedliche Substratspezifität aufweist als die erste Acyltransferase, oder

10

- (j) Deletieren zumindest einer Domänen-codierender Nucleinsäuresequenz gemäß Anspruch 7, oder

15

- (k) Integrieren zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 in eine Modul-codierende Nucleinsäuresequenz gemäß Anspruch 7, oder

- (l) Mutagenisieren zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7,

20

und Exprimieren der rekombinierten Nucleinsäuresequenz in einer Wirtszelle unter Bedingungen, welche die Synthese eines Spinosyn-Derivates oder einer Spinosyn-Vorstufe erlauben.

25

59. Verwendung einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 zum Identifizieren, Inaktivieren und/oder Modifizieren von Genen der Spinosyn-Biosynthese.

30

60. Verwendung einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 zum Erzeugen einer Bibliothek aus Polyketidsynthasen.

61. Verfahren zum Anfügen eines Forosamin-Zuckerrestes an das Spinosyn-Aglycon oder das Spinosyn-17-Pseudoaglycon, umfassend die folgenden Schritte:

- 5
- (a) Übertragen einer Nucleinsäure gemäß SEQ ID NOS: 23, 25, 29, 31, 33, 35 und 37 in eine Wirtszelle,
 - (b) Zufügen des Spinosyn-Aglycons oder Spinosyn-17-Pseudoaglycons, und
 - (c) Kultivieren unter Bedingungen, die zu einem aktiven Stoffwechsel der Zelle führen.
- 10

62. Verfahren zum Anfügen eines Trimethyl-Rhamnose-Zuckerrestes an das Spinosyn-Aglycon, umfassend die folgenden Schritte:

- 15
- (a) Übertragen einer Nucleinsäure gemäß SEQ ID NO: 7, 9, 11, 13, 17 und/oder 19 in eine Wirtszelle,
 - (b) Zufügen des Spinosyn-Aglycons oder Spinosyn-17-Pseudoaglycons, und
 - (c) Kultivieren unter Bedingungen, die zu einem aktiven Stoffwechsel der Zelle führen.
- 20

63. Verfahren gemäß Anspruch 62, dadurch gekennzeichnet, dass im Schritt (a) Nucleinsäuren gemäß SEQ ID NOS: 9, 11, 13 und 17 übertragen werden.

Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren

Z u s a m m e n f a s s u n g

Die vorliegende Erfindung betrifft Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren, sowie die entsprechenden Enzyme per se. Weiterhin betrifft die Erfindung Verfahren zum Herstellen von Spinosyn-Derivaten und -Vorstufen.

Abbildung 1: Reaktionsweg für die Biosynthese des N-Acetylglucosamins (NAG) aus Glucose-1-P

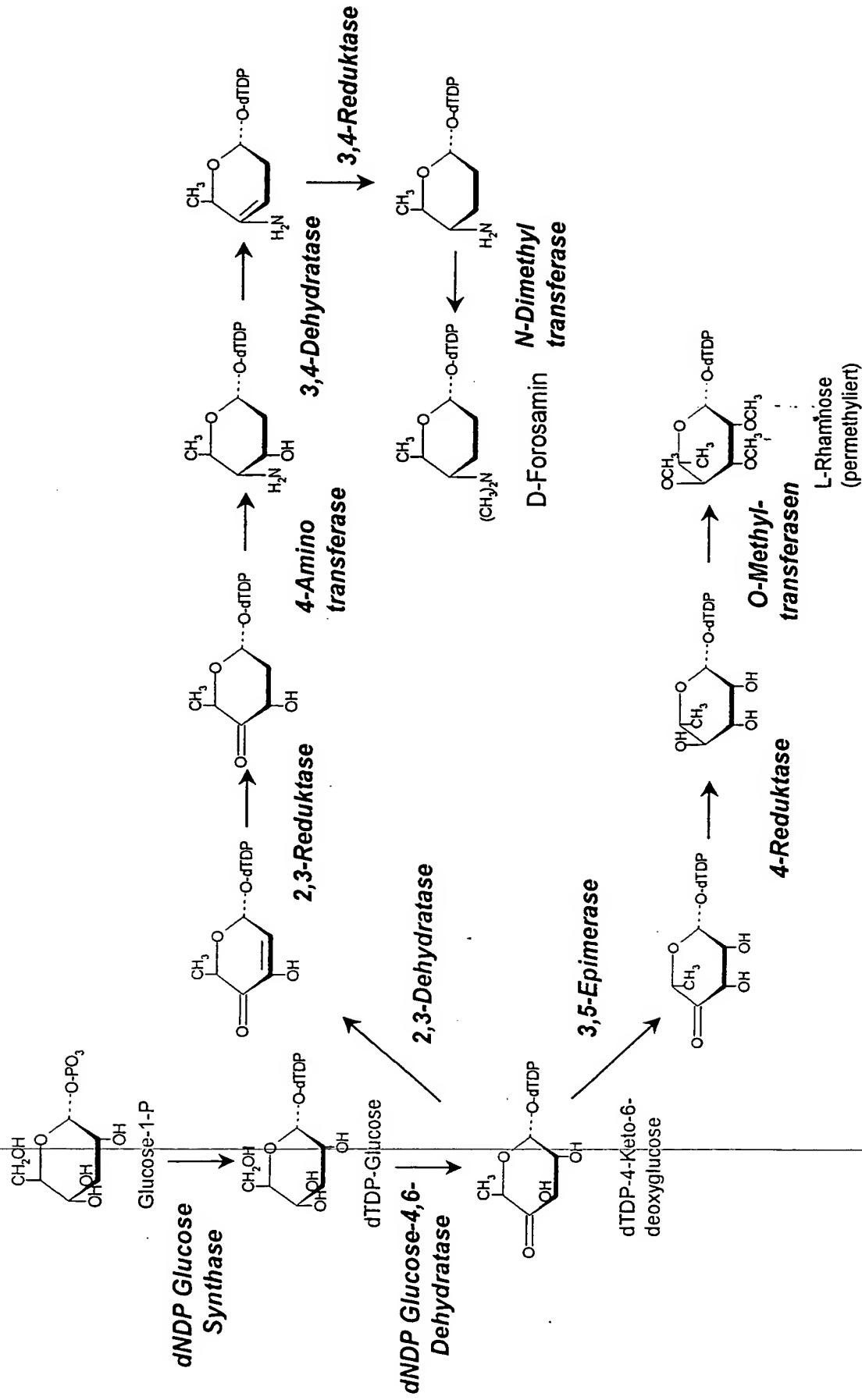
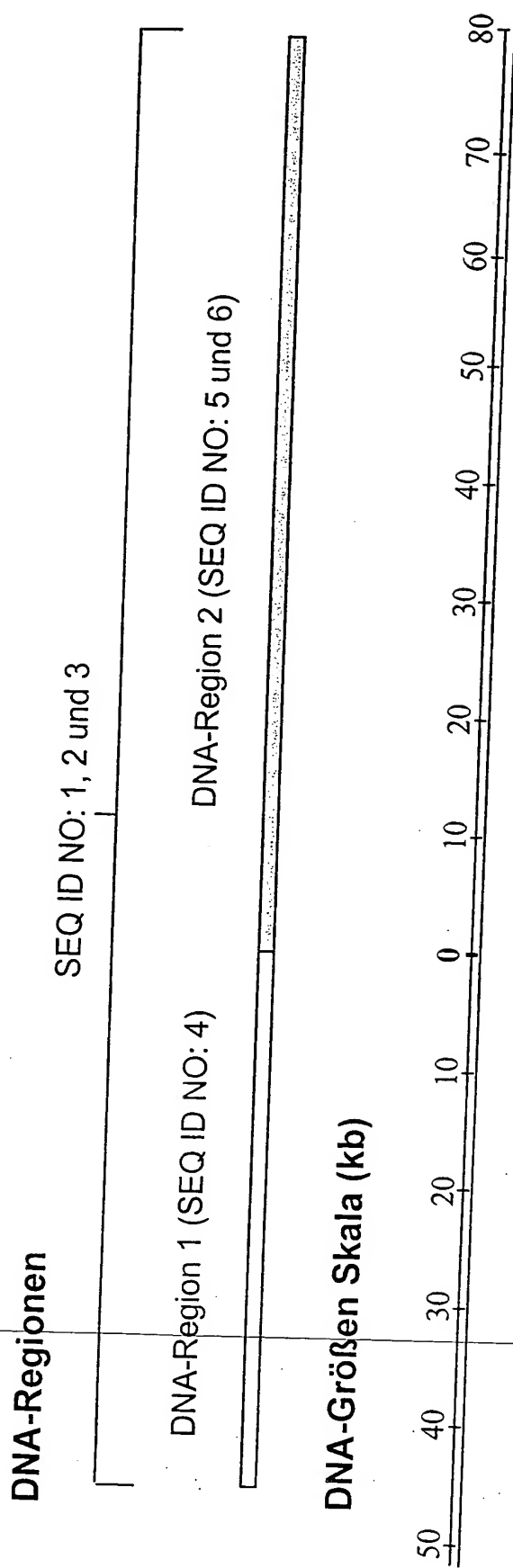


Abbildung 2: Lage, der Spinosyn Biosynthesepunkt oder indirekt beteiligten DNA-Regionen 1 und 2 sowie Lage und Bezeichnung der zur Sequenzierung herangezogenen überlappenden Cosmidklone



Cosmid-Bezeichnung, sowie Größe, Position und Überlappung von Insert-DNA

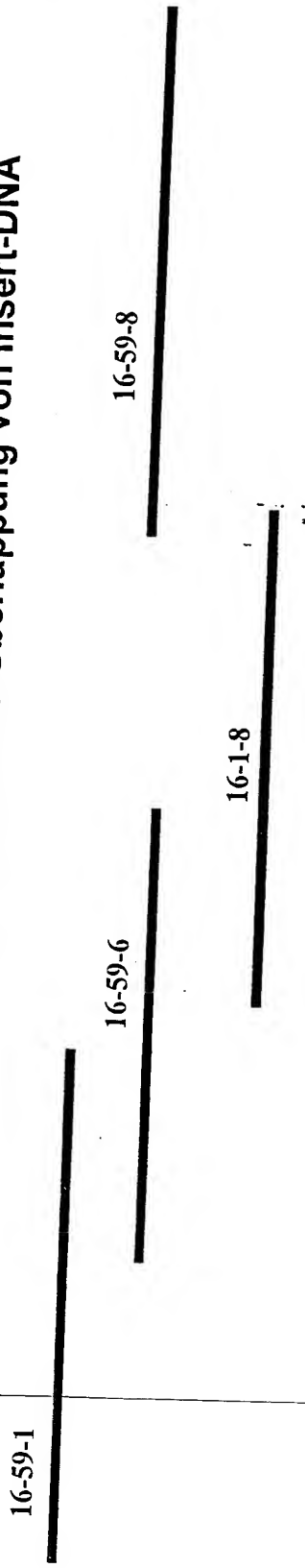


Abbildung 3: **Electroporation herangeführte Cosmidklone**

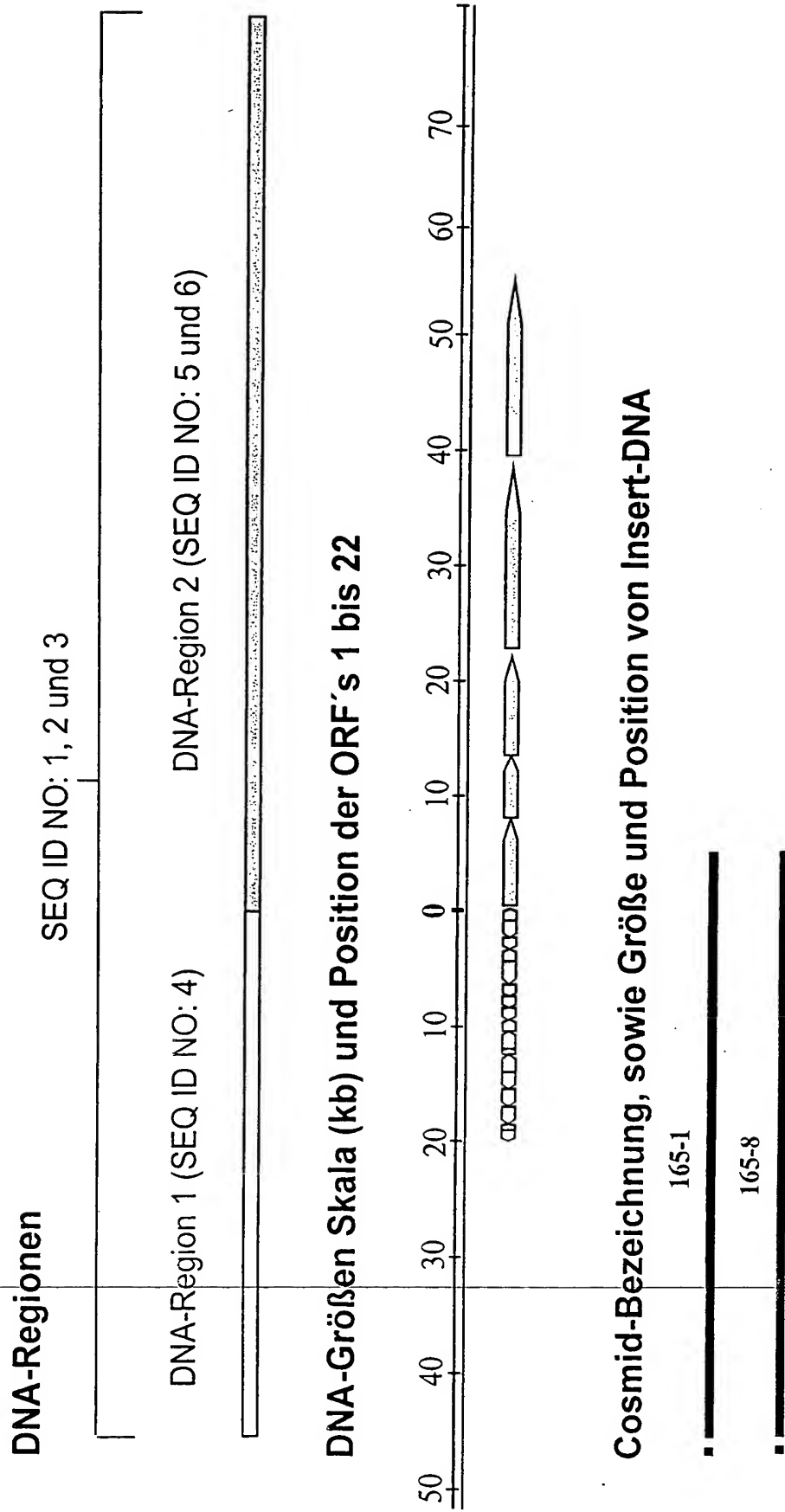


Abbildung 4: Darstellung offener Leserahmen
der DNA-Region 3 (SEQ ID NO: 51) auf Cosmid 16-2-2

SEQ ID NO: 51

DNA-Größen Skala (kb) und Nucleotidposition

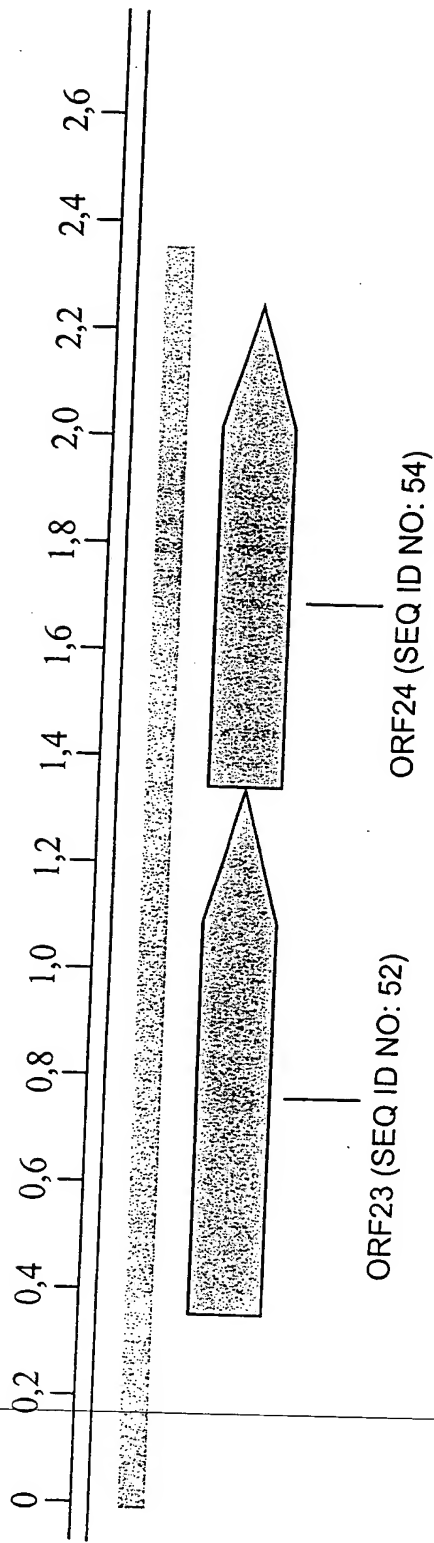


Abbildung 5: Darstellung offener Leserahmen der DNA-Regionen 1 und 2, die direkt oder indirekt an der Spinosyn-Biosynthese involviert sind

DNA-Region

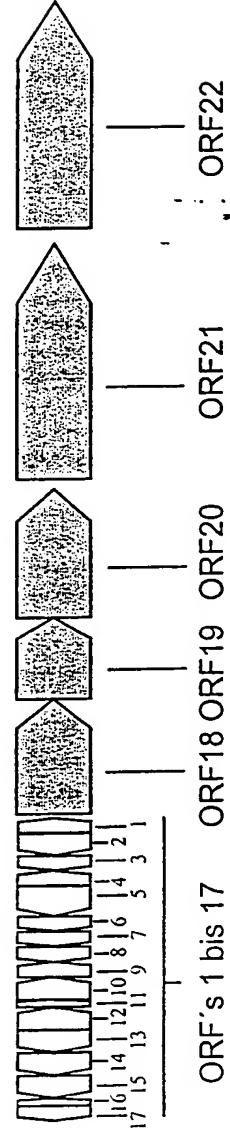
DNA-Region 1 (Ausschnitt)

DNA-Region 2 (Ausschnitt)

DNA-Größen Skala (kb) und Nucleotidposition



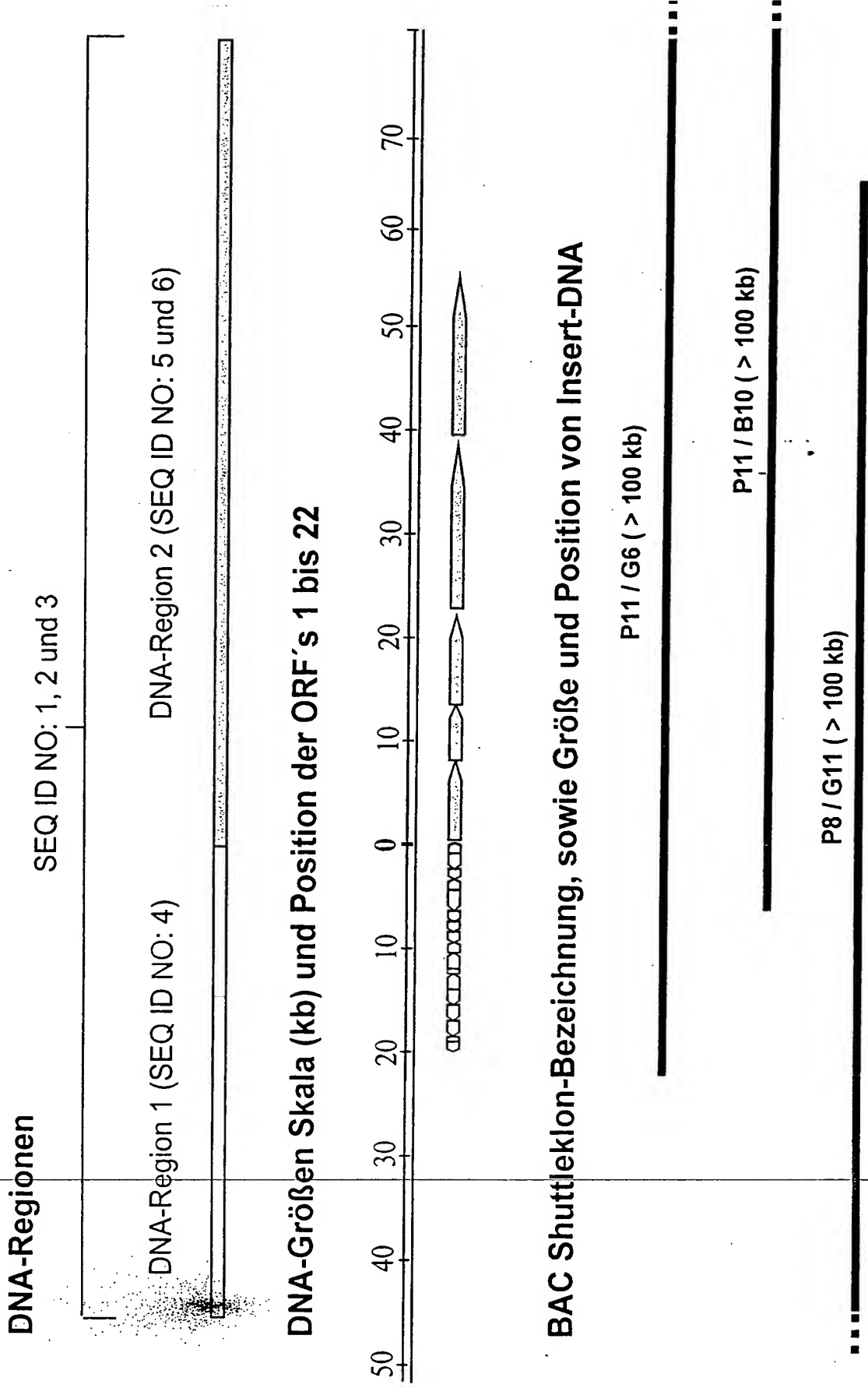
Offene Leserahmen (ORF's)



Stellung offener LeserInnen

[illegible]

Abbildung 7: Darstellung von Spinosyn Biosynthesegenen BAC Shuttleklonen



SEQUENZPROTOKOLL

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<120> Nucleinsäuren, die für Enzymaktivitäten der
Spinosyn-Biosynthese codieren

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<170> PatentIn Ver. 2.1

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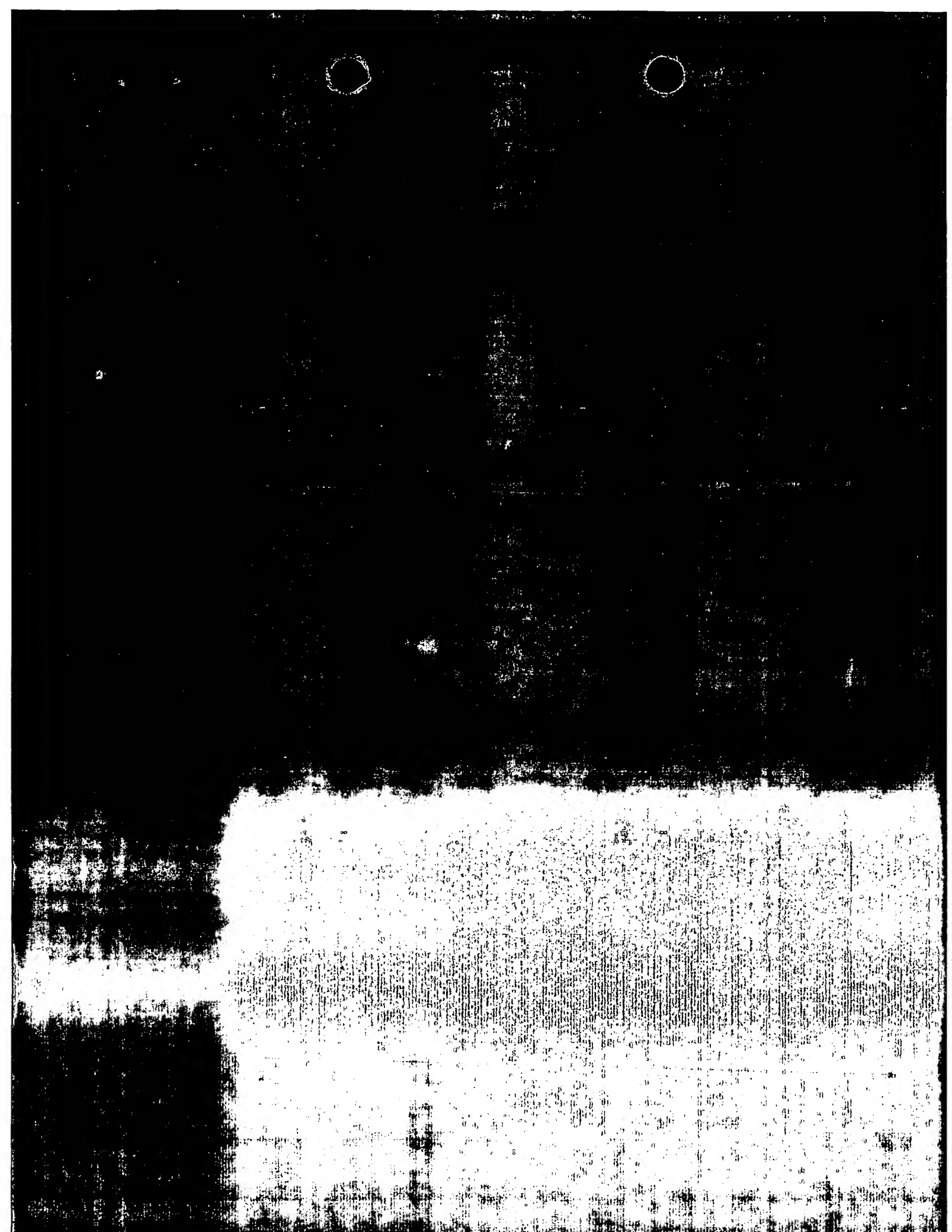
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<213> Saccharopolyspora spinosa

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<223> ORF1; O-Methyltransferase

<400> 7

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 Val Leu Pro Gly Gly Ala Pro Thr Ser Gln Gln Val Gly Gln Met Tyr
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gac ctg gtc acg ccg ttg ctg aac tcg gtc gcg ggc ggc ccc tgc gcc 96
 Asp Leu Val Thr Pro Leu Leu Asn Ser Val Ala Gly Gly Pro Cys Ala
 20 25 30

~~atc cac cac ggc tac tgg gag aac gac ggg cgg gct tcc tgg cag cag 144~~
 Ile His His Gly Tyr Trp Glu Asn Asp Gly Arg Ala Ser Trp Gln Gln
 35 40 45

gcc gcc gac cgg ctc acc gac ctt gtc gcc gaa cgg acc gtg ctc gat 192
 Ala Ala Asp Arg Leu Thr Asp Leu Val Ala Glu Arg Thr Val Leu Asp
 50 55 60

ggc ggc gtt cga ctg ctc gat gtg ggg tgc ggt acc gga caa cca gcg 240
 Gly Gly Val Arg Leu Leu Asp Val Gly Cys Gly Thr Gly Gln Pro Ala
 65 70 75 80

ctg cgc gtc gcg cgc gac aac gcg atc cag atc acc ggc atc acc gtc 288
 Leu Arg Val Ala Arg Asp Asn Ala Ile Gln Ile Thr Gly Ile Thr Val
 85 90 95

agc cag gtg caa gtg gcc atc gcc gct gat tgc gca cgc gaa cgc gga 336
 Ser Gln Val Gln Val Ala Ile Ala Ala Asp Cys Ala Arg Glu Arg Gly
 100 105 110

cta agc cac cgg gtg gac ttc tcg tgc gtc gat gcc atg tcc ctg ccg 384
 Leu Ser His Arg Val Asp Phe Ser Cys Val Asp Ala Met Ser Leu Pro
 115 120 125

tac ccg gac aat gct ttc gac gcc gcc tgg gcc atg cag tcg ctg ttg 432
 Tyr Pro Asp Asn Ala Phe Asp Ala Ala Trp Ala Met Gln Ser Leu Leu
 130 135 140

gag atg tcc gaa ccg gac cgt gcc atc cgg gaa atc ctt cga gta ctc 480
 Glu Met Ser Glu Pro Asp Arg Ala Ile Arg Glu Ile Leu Arg Val Leu
 145 150 155 160

aaa ccc ggt ggc atc ctc ggc gtc acc gag gtc gtc aaa cga gaa gcg 528
 Lys Pro Gly Gly Ile Leu Gly Val Thr Glu Val Val Lys Arg Glu Ala
 165 170 175

ggc ggc ggg atg ccg gtg tcc ggg gac agg tgg ccg acc ggc ctt ccg 576
 Gly Gly Gly Met Pro Val Ser Gly Asp Arg Trp Pro Thr Gly Leu Arg
 180 185 190

atc tgc ctg gct gag caa ctt ctg gaa tcg ctg cgt gca gcg ggg ttc 624
 Ile Cys Leu Ala Glu Gln Leu Leu Glu Ser Leu Arg Ala Ala Gly Phe
 195 200 205

gag atc ctc gat tgg gag gac gtg tcg tcg agg acc ccg tac ttc atg 672
 Glu Ile Leu Asp Trp Glu Asp Val Ser Ser Arg Thr Arg Tyr Phe Met
 210 215 220

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 Pro Gln Phe Ala Glu Glu Leu Ala Ala His Gln His Gly Ile Ala Asp
 225 230 235 240

agg tac ggg ccg gct gtc gcc ggc tgg gcc gcc gcg gtc tgc gat tat 768
 Arg Tyr Gly Pro Ala Val Ala Gly Trp Ala Ala Ala Val Cys Asp Tyr
 245 250 255

gag aaa tat gcc cac gac atg ggc tat gcg att ctg acg gcg cgg aag 816
 Glu Lys Tyr Ala His Asp Met Gly Tyr Ala Ile Leu Thr Ala Arg Lys
 260 265 270

ccg gtc ggc tga 828
 Pro Val Gly
 275

<210> 8
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 <212> PRT
 <213> Saccharopolyspora spinosa

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Ile His His Gly Tyr Trp Glu Asn Asp Gly Arg Ala Ser Trp Gln Gln
 35 40 45

Ala Ala Asp Arg Leu Thr Asp Leu Val Ala Glu Arg Thr Val Leu Asp
 50 55 60

Gly Gly Val Arg Leu Leu Asp Val Gly Cys Gly Thr Gly Gln Pro Ala
 65 70 75 80

Leu Arg Val Ala Arg Asp Asn Ala Ile Gln Ile Thr Gly Ile Thr Val
 85 90 95

Ser Gln Val Gln Val Ala Ile Ala Ala Asp Cys Ala Arg Glu Arg Gly
 100 105 110

Leu Ser His Arg Val Asp Phe Ser Cys Val Asp Ala Met Ser Leu Pro
 115 120 125

Tyr Pro Asp Asn Ala Phe Asp Ala Ala Trp Ala Met Gln Ser Leu Leu
 130 135 140

Glu Met Ser Glu Pro Asp Arg Ala Ile Arg Glu Ile Leu Arg Val Leu
 145 150 155 160

Lys Pro Gly Gly Ile Leu Gly Val Thr Glu Val Val Lys Arg Glu Ala
 165 170 175

Gly Gly Gly Met Pro Val Ser Gly Asp Arg Trp Pro Thr Gly Leu Arg
 180 185 190

Ile Cys Leu Ala Glu Gln Leu Leu Glu Ser Leu Arg Ala Ala Gly Phe
 195 200 205

Glu Ile Leu Asp Trp Glu Asp Val Ser Ser Arg Thr Arg Tyr Phe Met
 210 215 220

Pro Gln Phe Ala Glu Glu Leu Ala Ala His Gln His Gly Ile Ala Asp
 225 230 235 240

Arg Tyr Gly Pro Ala Val Ala Gly Trp Ala Ala Ala Val Cys Asp Tyr
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Glu Lys Tyr Ala His Asp Met Gly Tyr Ala Ile Leu Thr Ala Arg Lys
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Pro Val Gly
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 <213> Saccharopolyspora spinosa

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 <223> ORF2; Glycosyltransferase

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atg gtg ccg ctg tgc tgg gcg ctg caa gca tcc ggg cac gag gtc ctg 96
 Met Val Pro Leu Cys Trp Ala Leu Gln Ala Ser Gly His Glu Val Leu
 20 25 30

atc gcc gca cca cca gag ctg cag gcg acc gcg cat ggt gca ggt ctc 144
 Ile Ala Ala Pro Pro Glu Leu Gln Ala Thr Ala His Gly Ala Gly Leu
 35 40 45

acc acg gcc ggg atc cgc ggg aac gac agg acc ggc gat acg ggt gga 192

Thr Thr Ala Gly Ile Arg Gly Asn Asp Arg Thr Gly Asn Thr Gly Gly
 50 55 60

acc acg cag ctg cgc ttt ccc aat ccg gcg ttc ggt cag cgc gac acc 240
 Thr Thr Gln Leu Arg Phe Pro Asn Pro Ala Phe Gly Gln Arg Asp Thr
 65 70 75 80

gag gca ggc cgg caa ctg tgg gag cag acc gcg tcc aat gtc gcg caa 288
 Glu Ala Gly Arg Gln Leu Trp Glu Gln Thr Ala Ser Asn Val Ala Gln
 85 90 95

agc tcg ctc gat cag ctc ccc gaa tac ctt cga ctg gcc gag gcc tgg 336
 Ser Ser Leu Asp Gln Leu Pro Glu Tyr Leu Arg Leu Ala Glu Ala Trp
 100 105 110

cga ccg tca gtg ctg ttg gtc gac gtc tgc gcg ctg atc ggc cgg gtg 384
 Arg Pro Ser Val Leu Leu Val Asp Val Cys Ala Leu Ile Gly Arg Val
 115 120 125

ctc ggc gga ttg ctc gac ctg ccg gtc gtg ctg cac cgc tgg gga gtc 432
 Leu Gly Gly Leu Leu Asp Leu Pro Val Val Leu His Arg Trp Gly Val
 130 135 140

gac ccc acc gca ggc ccc ttc agc gat cga gcc cac gag ttg ctt gac 480
 Asp Pro Thr Ala Gly Pro Phe Ser Asp Arg Ala His Glu Leu Leu Asp
 145 150 155 160

ccg gtg tgc cgg cac cac gga ctg acc ggc ctg ccc act ccc gag ctc 528
 Pro Val Cys Arg His His Gly Leu Thr Gly Leu Pro Thr Pro Glu Leu
 165 170 175

atc ctc gat ccc tgt ccg ccg agc ctg caa gca agc gac gcg ccg caa 576
 Ile Leu Asp Pro Cys Pro Pro Ser Leu Gln Ala Ser Asp Ala Pro Gln
 180 185 190

ggc gca ccg gtc cag tac gtg ccg tac aac gga agc ggc gca ttc ccg 624
 Gly Ala Pro Val Gln Tyr Val Pro Tyr Asn Gly Ser Gly Ala Phe Pro
 195 200 205

gca tgg ggc gcg gcg cgc acc tca gca cgg cgg gtc tgc atc tgc atg 672
 Ala Trp Gly Ala Ala Arg Thr Ser Ala Arg Arg Val Cys Ile Cys Met
 210 215 220

ggc cgc atg gtg ctg aac gcc acc ggg ccg gct ccg ctg ctg cgc gca 720
 Gly Arg Met Val Leu Asn Ala Thr Gly Pro Ala Pro Leu Leu Arg Ala
 225 230 235 240

gta gcg gct gcc acc gag ttg ccc ggc gtc gag gcc gtg atc gcc gtt 768

Val Ala Ala Ala Thr Glu Leu Pro Gly Val Glu Ala Val Ile Ala Val
 245 250 255

ccc ccc gag cac cgg gca ctt ctc acc gac cta ccc gac aac gcc cgg 816
 Pro Pro Glu His Arg Ala Leu Leu Thr Asp Leu Pro Asp Asn Ala Arg
 260 265 270

atc gcc gaa tcg gtc ccg ctc aac ctg ttc ctg cgt acc tgc gag ctg 864
 Ile Ala Glu Ser Val Pro Leu Asn Leu Phe Leu Arg Thr Cys Glu Leu
 275 280 285

gtc atc tgc gcg ggc ggc tcg gga acg gca ttc acc gcg acc cga ctc 912
 Val Ile Cys Ala Gly Gly Ser Gly Thr Ala Phe Thr Ala Thr Arg Leu
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ggc atc ccg caa ctc gtg ctt ccc cag tac ttc gac cag ttc gac tac 960
 Gly Ile Pro Gln Leu Val Leu Pro Gln Tyr Phe Asp Gln Phe Asp Tyr
 305 310 315 320

gcg cgc aac ctc gcc gct gcc ggg gcg ggc atc tgc ttg ccg gat gag 1008
 Ala Arg Asn Leu Ala Ala Ala Gly Ala Gly Ile Cys Leu Pro Asp Glu
 325 330 335

cag gcc cag tcc gac cac gaa cag ttc acc gac tca atc gca acg gtg 1056
 Gln Ala Gln Ser Asp His Glu Gln Phe Thr Asp Ser Ile Ala Thr Val
 340 345 350

ctc ggc gac acc ggc ttc gct gct gcg gca atc aaa ctc agc gac gag 1104
 Leu Gly Asp Thr Gly Phe Ala Ala Ala Ala Ile Lys Leu Ser Asp Glu
 355 360 365

atc acg gcc atg ccc cat ccc gcc gcg ctg gtg cgg acg ctg gag aac 1152
 Ile Thr Ala Met Pro His Pro Ala Ala Leu Val Arg Thr Leu Glu Asn
 370 375 380

act gcg gcc atc cgt gcc tga 1173
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<210> 10

<211> 390

<212> PRT

<213> Saccharopolyspora spinosa

<400> 10

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Met Val Pro Leu Cys Trp Ala Leu Gln Ala Ser Gly His Glu Val Leu
20 25 30

Ile Ala Ala Pro Pro Glu Leu Gln Ala Thr Ala His Gly Ala Gly Leu
35 40 45

Thr Thr Ala Gly Ile Arg Gly Asn Asp Arg Thr Gly Asp Thr Gly Gly
50 55 60

Thr Thr Gln Leu Arg Phe Pro Asn Pro Ala Phe Gly Gln Arg Asp Thr
65 70 75 80

Glu Ala Gly Arg Gln Leu Trp Glu Gln Thr Ala Ser Asn Val Ala Gln
85 90 95

Ser Ser Leu Asp Gln Leu Pro Glu Tyr Leu Arg Leu Ala Glu Ala Trp
100 105 110

Arg Pro Ser Val Leu Leu Val Asp Val Cys Ala Leu Ile Gly Arg Val
115 120 125

Leu Gly Gly Leu Leu Asp Leu Pro Val Val Leu His Arg Trp Gly Val
130 135 140

Asp Pro Thr Ala Gly Pro Phe Ser Asp Arg Ala His Glu Leu Leu Asp
145 150 155 160

Pro Val Cys Arg His His Gly Leu Thr Gly Leu Pro Thr Pro Glu Leu
165 170 175

Ile Leu Asp Pro Cys Pro Pro Ser Leu Gln Ala Ser Asp Ala Pro Gln
180 185 190

Gly Ala Pro Val Gln Tyr Val Pro Tyr Asn Gly Ser Gly Ala Phe Pro
195 200 205

Ala Trp Gly Ala Ala Arg Thr Ser Ala Arg Arg Val Cys Ile Cys Met
210 215 220

Gly Arg Met Val Leu Asn Ala Thr Gly Pro Ala Pro Leu Leu Arg Ala
225 230 235 240

Val Ala Ala Ala Thr Glu Leu Pro Gly Val Glu Ala Val Ile Ala Val
245 250 255

Pro Pro Glu His Arg Ala Leu Leu Thr Asp Leu Pro Asp Asn Ala Arg
260 265 270

Ile Ala Glu Ser Val Pro Leu Asn Leu Phe Leu Arg Thr Cys Glu Leu
 275 280 285

Val Ile Cys Ala Gly Gly Ser Gly Thr Ala Phe Thr Ala Thr Arg Leu
 290 295 300

Gly Ile Pro Gln Leu Val Leu Pro Gln Tyr Phe Asp Gln Phe Asp Tyr
 305 310 315 320

Ala Arg Asn Leu Ala Ala Ala Gly Ala Gly Ile Cys Leu Pro Asp Glu
 325 330 335

Gln Ala Gln Ser Asp His Glu Gln Phe Thr Asp Ser Ile Ala Thr Val
 340 345 350

Leu Gly Asp Thr Gly Phe Ala Ala Ala Ala Ile Lys Leu Ser Asp Glu
 355 360 365

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 370 375 380

Thr Ala Ala Ile Arg Ala
 385 390

<210> 11
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 <213> Saccharopolyspora spinosa

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 <223> ORF3; O-Methyltransferase

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 Met Pro Ser Gln Asn Ala Leu Tyr Leu Asp Leu Leu Lys Lys Val Leu
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acc aac acg att tac agt gat cgg ccg cat ccg aac gcc tgg cag gac 96
 Thr Asn Thr Ile Tyr Ser Asp Arg Pro His Pro Asn Ala Trp Gln Asp
 20 25 30

aac acc gac tac agg cag gcc gct cgg gcc aaa ggc acg gac tgg cca 144
 Asn Thr Asp Tyr Arg Gln Ala Ala Arg Ala Lys Gly Thr Asp Trp Pro

act gtc gcg cac acg atg atc ggt ctg gag cgg ctg gac aac ctc cag 192
 Thr Val Ala His Thr Met Ile Gly Leu Glu Arg Leu Asp Asn Leu Gln
 50 55 60

cac tgc gtg gaa gcc gtg ctc gca gac ggt gtt ccc ggg gat ttc gcc 240
 His Cys Val Glu Ala Val Leu Ala Asp Gly Val Pro Gly Asp Phe Ala
 65 70 75 80

gag acc ggt gtc tgg cgg ggc ggc gca tgc atc ttc atg cgc gcg gtt 288
 Glu Thr Gly Val Trp Arg Gly Gly Ala Cys Ile Phe Met Arg Ala Val
 85 90 95

ctc cag gca ttc gga gat acc gga cgt acc gtc tgg gta gtg gat tcc 336
 Leu Gln Ala Phe Gly Asp Thr Gly Arg Thr Val Trp Val Val Asp Ser
 100 105 110

ttc cag gga atg ccg gaa agc tct gcg caa gac cac caa gcg gac cag 384
 Phe Gln Gly Met Pro Glu Ser Ser Ala Gln Asp His Gln Ala Asp Gln
 115 120 125

gct atg gcg ctg cac gag tac aac gac gtg ctt ggc gta tcg ctt gag 432
 Ala Met Ala Leu His Glu Tyr Asn Asp Val Leu Gly Val Ser Leu Glu
 130 135 140

acc gtc cgg cag aac ttc gcc cgc tac ggg ctg ctc gac gaa cag gtc 480
 Thr Val Arg Gln Asn Phe Ala Arg Tyr Gly Leu Leu Asp Glu Gln Val
 145 150 155 160

agg ttc ctc ccc ggc tgg ttc cgg gac acc ttg ccc acc gcc ccc atc 528
 Arg Phe Leu Pro Gly Trp Phe Arg Asp Thr Leu Pro Thr Ala Pro Ile
 165 170 175

cag gaa ctc gcc gtg cta cga ctc gac ggc gac ctc tac gaa tcc aca 576
 Gln Glu Leu Ala Val Leu Arg Leu Asp Gly Asp Leu Tyr Glu Ser Thr
 180 185 190

atg gac tca ttg cgg aac ctg tac ccg aag ctc tcg ccg ggc gga ttc 624
 Met Asp Ser Leu Arg Asn Leu Tyr Pro Lys Leu Ser Pro Gly Gly Phe
 195 200 205

gtc atc atc gac gac tat ttt ctg ccg tcc tgc cag gac gcg gtg aag 672
 Val Ile Ile Asp Asp Tyr Phe Leu Pro Ser Cys Gln Asp Ala Val Lys
 210 215 220

ggg ttc cgc gcg gaa ctc ggg atc acg gaa ccc atc cac gac atc gac 720
 Gly Phe Arg Ala Glu Leu Gly Ile Thr Glu Pro Ile His Asp Ile Asp

225

230

235

240

ggc acg ggc gcc tac tgg cgc cgc agc tgg tga
 Gly Thr Gly Ala Tyr Trp Arg Arg Ser Trp
 245 250

753

<210> 12

<211> 250

<212> PRT

<213> *Saccharopolyspora spinosa*

<400> 12

Met Pro Ser Gln Asn Ala Leu Tyr Leu Asp Leu Leu Lys Lys Val Leu
 1 5 10 15

Thr Asn Thr Ile Tyr Ser Asp Arg Pro His Pro Asn Ala Trp Gln Asp
 20 25 30

Asn Thr Asp Tyr Arg Gln Ala Ala Arg Ala Lys Gly Thr Asp Trp Pro
 35 40 45

Thr Val Ala His Thr Met Ile Gly Leu Glu Arg Leu Asp Asn Leu Gln
 50 55 60

His Cys Val Glu Ala Val Leu Ala Asp Gly Val Pro Gly Asp Phe Ala
 65 70 75 80

Glu Thr Gly Val Trp Arg Gly Gly Ala Cys Ile Phe Met Arg Ala Val
 85 90 95

Leu Gln Ala Phe Gly Asp Thr Gly Arg Thr Val Trp Val Val Asp Ser
 100 105 110

Phe Gln Gly Met Pro Glu Ser Ser Ala Gln Asp His Gln Ala Asp Gln
 115 120 125

Ala Met Ala Leu His Glu Tyr Asn Asp Val Leu Gly Val Ser Leu Glu
 130 135 140

Thr Val Arg Gln Asn Phe Ala Arg Tyr Gly Leu Leu Asp Glu Gln Val
 145 150 155 160

Arg Phe Leu Pro Gly Trp Phe Arg Asp Thr Leu Pro Thr Ala Pro Ile
 165 170 175

Gln Glu Leu Ala Val Leu Arg Leu Asp Gly Asp Leu Tyr Glu Ser Thr
 180 185 190

Met Asp Ser Leu Arg Asn Leu Tyr Pro Lys Leu Ser Pro Gly Gly Phe
 195 200 205

Val Ile Ile Asp Asp Tyr Phe Leu Pro Ser Cys Gln Asp Ala Val Lys
 210 215 220

Gly Phe Arg Ala Glu Leu Gly Ile Thr Glu Pro Ile His Asp Ile Asp
 225 230 235 240

Gly Thr Gly Ala Tyr Trp Arg Arg Ser Trp
 245 250

<210> 13

<211> 1188

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1185)

<223> ORF4; O-Methyltransferase

<400> 13

atg agt gag atc gca gtt gcc ccc tgg tcg gtg gtg gag cgt ttg ctg 48
 Met Ser Glu Ile Ala Val Ala Pro Trp Ser Val Val Glu Arg Leu Leu
 1 5 10 15

ctc gcg gcg ggt gcg ggc ccg gcg aag ctc cag gaa gca gtg cag gtg 96
 Leu Ala Ala Gly Ala Gly Pro Ala Lys Leu Gln Glu Ala Val Gln Val
 20 25 30

gcc gga ctg gac gcg gtg gcc gac gcc atc gtc gac gaa ctc gtc gta 144
 Ala Gly Leu Asp Ala Val Ala Asp Ala Ile Val Asp Glu Leu Val Val
 35 40 45

cgc tgc gat ccg ctg tcg ttg gac gag tcg gtg cga atc ggc ctg gag 192
 Arg Cys Asp Pro Leu Ser Leu Asp Glu Ser Val Arg Ile Gly Leu Glu
 50 55 60

atc act tct ggc gct cag ctg gtc cgg aga acc gtt gag ctc gat cac 240
 Ile Thr Ser Gly Ala Gln Leu Val Arg Arg Thr Val Glu Leu Asp His
 65 70 75 80

gca ggc ctg cgg ctc gcg gcg gtc gcc gaa gca gct gct gtt ctc cgg 288
 Ala Gly Leu Arg Leu Ala Ala Val Ala Glu Ala Ala Val Leu Arg

ttc gac gcg gtg gat ctg ctg gaa ggg ctc ttc ggc ccg gtt gac ggc 336
 Phe Asp Ala Val Asp Leu Leu Glu Gly Leu Phe Gly Pro Val Asp Gly
 100 105 110

agg cgg cac aac agc cgt gaa gtc cgc tgg tcg gac agc atg acg cag 384
 Arg Arg His Asn Ser Arg Glu Val Arg Trp Ser Asp Ser Met Thr Gln
 115 120 125

ttc tcg ccc gac cag ggc ctc gcc ggc gcg cag cgc ctg ctg gcg ttc 432
 Phe Ser Pro Asp Gln Gly Leu Ala Gly Ala Gln Arg Leu Leu Ala Phe
 130 135 140

cgg aac agg gtg tcc acc gcg gtg cac gcc gtg ctg gcc gca gcc gcc 480
 Arg Asn Arg Val Ser Thr Ala Val His Ala Val Leu Ala Ala Ala Ala
 145 150 155 160

acc agg cgc gcg gac ctc ggt gcg ctg gca gtc cgc tac gga tcc gac 528
 Thr Arg Arg Ala Asp Leu Gly Ala Leu Ala Val Arg Tyr Gly Ser Asp
 165 170 175

aaa tgg gcg gac ctg cac tgg tac acc gaa cac tac gag cac cac ttc 576
 Lys Trp Ala Asp Leu His Trp Tyr Thr Glu His Tyr Glu His His Phe
 180 185 190

tcc cga ttc cag gat gcc ccg gtg cga gtg ttg gaa ata gga atc ggt 624
 Ser Arg Phe Gln Asp Ala Pro Val Arg Val Leu Glu Ile Gly Ile Gly
 195 200 205

ggt tat cac gca ccc gaa ctc ggt ggt gct tcg ctg cgc atg tgg cag 672
 Gly Tyr His Ala Pro Glu Leu Gly Gly Ala Ser Leu Arg Met Trp Gln
 210 215 220

cgg tac ttc cgg cga ggt ctc gtt tac ggg ctg gac att ttc gag aaa 720
 Arg Tyr Phe Arg Arg Gly Leu Val Tyr Gly Leu Asp Ile Phe Glu Lys
 225 230 235 240

gcc ggg aac gaa ggg cac cga gtg cga aag ctg cga ggt gac cag agc 768
 Ala Gly Asn Glu Gly His Arg Val Arg Lys Leu Arg Gly Asp Gln Ser
 245 250 255

gat gcg gaa ttc ctg gaa gac atg gcg ggg aag atc ggg ccg ttc gac 816
 Asp Ala Glu Phe Leu Glu Asp Met Ala Gly Lys Ile Gly Pro Phe Asp
 260 265 270

att gtc atc gac gac ggc agc cat gtc aac gac cac gtc aag aaa tcc 864
 Ile Val Ile Asp Asp Gly Ser His Val Asn Asp His Val Lys Lys Ser

275

280

285

ttc caa tcc ctg ttt ccg cac gtc cgc cca ggt ggt ttg tac gtc atc 912
 Phe Gln Ser Leu Phe Pro His Val Arg Pro Gly Gly Leu Tyr Val Ile
 290 295 300

gag gat ctc cag acg gcg tac tgg ccc ggc tac ggc ggt cgc gat ggg 960
 Glu Asp Leu Gln Thr Ala Tyr Trp Pro Gly Tyr Gly Gly Arg Asp Gly
 305 310 315 320

gaa ccc gcg gcc cag cgc acc tcg atc gac atg ctc aaa gaa ctg atc 1008
 Glu Pro Ala Ala Gln Arg Thr Ser Ile Asp Met Leu Lys Glu Leu Ile
 325 330 335

gac ggc ctg cat tat cag gag cgc gaa tcg cgg tgc ggg acc gag ccc 1056
 Asp Gly Leu His Tyr Gln Glu Arg Glu Ser Arg Cys Gly Thr Glu Pro
 340 345 350

tcc tac acg gaa cgg aac gtg gcg gcc ctg cac ttc tac cac aac ctg 1104
 Ser Tyr Thr Glu Arg Asn Val Ala Ala Leu His Phe Tyr His Asn Leu
 355 360 365

gta ttc gtg gag aaa ggg ctc aac gct gag cct gcc gcg ccg ggg ttc 1152
 Val Phe Val Glu Lys Gly Leu Asn Ala Glu Pro Ala Ala Pro Gly Phe
 370 375 380

gtg ccc cgg caa gcg ctc ggc gtc gag gac ggc tga 1188
 Val Pro Arg Gln Ala Leu Gly Val Glu Asp Gly
 385 390 395

<210> 14

<211> 395

<212> PRT

<213> Saccharopolyspora spinosa

<400> 14

Met Ser Glu Ile Ala Val Ala Pro Trp Ser Val Val Glu Arg Leu Leu
 1 5 10 15

Leu Ala Ala Gly Ala Gly Pro Ala Lys Leu Gln Glu Ala Val Gln Val
 20 25 30

Ala Gly Leu Asp Ala Val Ala Asp Ala Ile Val Asp Glu Leu Val Val
 35 40 45

Arg Cys Asp Pro Leu Ser Leu Asp Glu Ser Val Arg Ile Gly Leu Glu
 50 55 60

Ile Thr Ser Gly Ala Gln Leu Val Arg Arg Thr Val Glu Leu Asp His
65 70 75 80

Ala Gly Leu Arg Leu Ala Ala Val Ala Glu Ala Ala Val Leu Arg
85 90 95

Phe Asp Ala Val Asp Leu Leu Glu Gly Leu Phe Gly Pro Val Asp Gly
100 105 110

Arg Arg His Asn Ser Arg Glu Val Arg Trp Ser Asp Ser Met Thr Gln
115 120 125

Phe Ser Pro Asp Gln Gly Leu Ala Gly Ala Gln Arg Leu Leu Ala Phe
130 135 140

Arg Asn Arg Val Ser Thr Ala Val His Ala Val Leu Ala Ala Ala Ala
145 150 155 160

Thr Arg Arg Ala Asp Leu Gly Ala Leu Ala Val Arg Tyr Gly Ser Asp
165 170 175

Lys Trp Ala Asp Leu His Trp Tyr Thr Glu His Tyr Glu His His Phe
180 185 190

Ser Arg Phe Gln Asp Ala Pro Val Arg Val Leu Glu Ile Gly Ile Gly
195 200 205

Gly Tyr His Ala Pro Glu Leu Gly Gly Ala Ser Leu Arg Met Trp Gln
210 215 220

Arg Tyr Phe Arg Arg Gly Leu Val Tyr Gly Leu Asp Ile Phe Glu Lys
225 230 235 240

Ala Gly Asn Glu Gly His Arg Val Arg Lys Leu Arg Gly Asp Gln Ser
245 250 255

Asp Ala Glu Phe Leu Glu Asp Met Ala Gly Lys Ile Gly Pro Phe Asp
260 265 270

Ile Val Ile Asp Asp Gly Ser His Val Asn Asp His Val Lys Lys Ser
275 280 285

Phe Gln Ser Leu Phe Pro His Val Arg Pro Gly Gly Leu Tyr Val Ile
290 295 300

Glu Asp Leu Gln Thr Ala Tyr Trp Pro Gly Tyr Gly Gly Arg Asp Gly
305 310 315 320

Glu Pro Ala Ala Gln Arg Thr Ser Ile Asp Met Leu Lys Glu Leu Ile
 325 330 335

Asp Gly Leu His Tyr Gln Glu Arg Glu Ser Arg Cys Gly Thr Glu Pro
 340 345 350

Ser Tyr Thr Glu Arg Asn Val Ala Ala Leu His Phe Tyr His Asn Leu
 355 360 365

Val Phe Val Glu Lys Gly Leu Asn Ala Glu Pro Ala Ala Pro Gly Phe
 370 375 380

Val Pro Arg Gln Ala Leu Gly Val Glu Asp Gly
 385 390 395

<210> 15

<211> 1620

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1617)

<223> ORF5; C-C verknüpfendes Enzym, Cyclisierungsenzym

<400> 15

atg atc tcg gct gcg ggc gaa caa agt gga cca gtc aga aaa gga ggg 48
 Met Ile Ser Ala Ala Gly Glu Gln Ser Gly Pro Val Arg Lys Gly Gly
 1 5 10 15

gcg gtg ccc gaa ttc cat gac ccg gca ccc atg aat cgt cga acc cca 96
 Ala Val Pro Glu Phe His Asp Pro Ala Pro Met Asn Arg Arg Thr Pro
 20 25 30

gga aca gag atc acc gtc gag ccc gac gat cct cgt tat ccg gac ctc 144
 Gly Thr Glu Ile Thr Val Glu Pro Asp Asp Pro Arg Tyr Pro Asp Leu
 35 40 45

~~gtc gtc ggg cac aac ccc cgt ttc acc gga aaa ccc gaa cgc atc cac 192~~
 Val Val Gly His Asn Pro Arg Phe Thr Gly Lys Pro Glu Arg Ile His
 50 55 60

atc gcc agc tcc gcc gaa gac gtc gtg cac gcc gtc gcc gac gcc gtg 240
 Ile Ala Ser Ser Ala Glu Asp Val Val His Ala Val Ala Asp Ala Val
 65 70 75 80

cgc acc ggc agg cgg gta ggg gtc cgc agc ggc ggg cac tgc ttc gag 288
 Arg Thr Gly Arg Arg Val Gly Val Arg Ser Gly Gly His Cys Phe Glu
 85 90 95

aat ctc gtt gcg gac ccg gcg atc cga gtg ctc gtc gac ctc tcc gag 336
 Asn Leu Val Ala Asp Pro Ala Ile Arg Val Leu Val Asp Leu Ser Glu
 100 105 110

ctc aac cgc gtg tac tac gac agc acg cgc ggg gca ttc gcg atc gag 384
 Leu Asn Arg Val Tyr Tyr Asp Ser Thr Arg Gly Ala Phe Ala Ile Glu
 115 120 125

gcg ggc gcc gcc ctc ggg cag gtg tac cga acc ctg ttc aag aac tgg 432
 Ala Gly Ala Ala Leu Gly Gln Val Tyr Arg Thr Leu Phe Lys Asn Trp
 130 135 140

ggc gtg acg atc ccg acc ggc gca tgt ccc ggg gtg ggc gca ggc ggg 480
 Gly Val Thr Ile Pro Thr Gly Ala Cys Pro Gly Val Gly Ala Gly Gly
 145 150 155 160

cac atc ctc ggc ggg gga tac ggc ccg ctg tcg cgc cga ttc ggt tcg 528
 His Ile Leu Gly Gly Gly Tyr Gly Pro Leu Ser Arg Arg Phe Gly Ser
 165 170 175

gtc gtc gac tac ctt caa ggc gtc gag gtc gtc gtg gtc gac cag gcc 576
 Val Val Asp Tyr Leu Gln Gly Val Glu Val Val Val Val Asp Gln Ala
 180 185 190

ggt gaa gtg cac atc gtc gag gcc gac cgg aac tcc acg ggc gcc ggt 624
 Gly Glu Val His Ile Val Glu Ala Asp Arg Asn Ser Thr Gly Ala Gly
 195 200 205

cac gac ttg tgg tgg gcg cac acc ggt ggc ggt ggc ggc aac ttc ggg 672
 His Asp Leu Trp Trp Ala His Thr Gly Gly Gly Gly Gly Asn Phe Gly
 210 215 220

atc gtc acc agg ttt tgg ctc cga acg ccg gac gtg gtc agc acc gac 720
 Ile Val Thr Arg Phe Trp Leu Arg Thr Pro Asp Val Val Ser Thr Asp
 225 230 235 240

~~gcc gca gag ctc ctg cca cgg ccg ccc gcg aca gtg ctg ctc cga tcg 768~~
~~Ala Ala Glu Leu Leu Pro Arg Pro Pro Ala Thr Val Leu Leu Arg Ser~~
~~245 250 255~~

ttc cac tgg ccg tgg cac gaa ctg aca gag cag tca ttc gcc gtg ctc 816
 Phe His Trp Pro Trp His Glu Leu Thr Glu Gln Ser Phe Ala Val Leu
 260 265 270

cta cag aac ttc ggc aat tgg tac gag cag cac agc gcg cct gaa tcc	864
Leu Gln Asn Phe Gly Asn Trp Tyr Glu Gln His Ser Ala Pro Glu Ser	
275 280 285	
acg caa ctc ggg ttg ttc agc acg ctc gtc tgc gca cac cgg caa gct	912
Thr Gln Leu Gly Leu Phe Ser Thr Leu Val Cys Ala His Arg Gln Ala	
290 295 300	
ggc tac gtc acg ctg aac gtt cac ctg gac ggc acg gat ccg aac gcg	960
Gly Tyr Val Thr Leu Asn Val His Leu Asp Gly Thr Asp Pro Asn Ala	
305 310 315 320	
gaa cgc acc ctg gcc gaa cac ctg tcg gcg atc aac gcc cag gtc ggc	1008
Glu Arg Thr Leu Ala Glu His Leu Ser Ala Ile Asn Ala Gln Val Gly	
325 330 335	
gtg act cca gcc gaa ggg ctg cgg gaa acc ctg ccg tgg ttg cga tcg	1056
Val Thr Pro Ala Glu Gly Leu Arg Glu Thr Leu Pro Trp Leu Arg Ser	
340 345 350	
acc cag gtg gcc ggg gcg atc gcc gaa ggc ggc gaa ccg ggc atg caa	1104
Thr Gln Val Ala Gly Ala Ile Ala Glu Gly Gly Glu Pro Gly Met Gln	
355 360 365	
cgg acc aag gtc aaa gcc gcc tac ttg cgc acc ggg ctg tcc gaa gct	1152
Arg Thr Lys Val Lys Ala Ala Tyr Leu Arg Thr Gly Leu Ser Glu Ala	
370 375 380	
caa cta gcc acg gtt tac cgg cgg ctg acc gtc tac gga tac gac aac	1200
Gln Leu Ala Thr Val Tyr Arg Arg Leu Thr Val Tyr Gly Tyr Asp Asn	
385 390 395 400	
cct gcg gcg gcg ctg ttg ctg ctc ggt tac ggc ggt atg gcg aat gcc	1248
Pro Ala Ala Ala Leu Leu Leu Gly Tyr Gly Gly Met Ala Asn Ala	
405 410 415	
gtg gct ccg tcg gcc acc gca ctc gct cag cgc gac tcg gtt ctc aaa	1296
Val Ala Pro Ser Ala Thr Ala Leu Ala Gln Arg Asp Ser Val Leu Lys	
420 425 430	
gcg ctg ttc gtc acg aac tgg tcg gag ccc gcc gag gac gag cgg cat	1344
Ala Leu Phe Val Thr Asn Trp Ser Glu Pro Ala Glu Asp Glu Arg His	
435 440 445	
ctg acc tgg att cgc ggt ttc tac cgc gag atg tac gcc gaa acc ggc	1392
Leu Thr Trp Ile Arg Gly Phe Tyr Arg Glu Met Tyr Ala Glu Thr Gly	
450 455 460	

gga gtt ccg gtg cca ggt acc cgt gtc gac ggc tcc tac atc aac tac 1440
 Gly Val Pro Val Pro Gly Thr Arg Val Asp Gly Ser Tyr Ile Asn Tyr
 465 470 475 480

ccg gac acc gac ttg gcc gat cca ttg tgg aac acc tcc ggt gtt gcc 1488
 Pro Asp Thr Asp Leu Ala Asp Pro Leu Trp Asn Thr Ser Gly Val Ala
 485 490 495

tgg cac gac ctg tac tac aaa gac aac tac ccg cgg ctg cag cgg gcc 1536
 Trp His Asp Leu Tyr Tyr Lys Asp Asn Tyr Pro Arg Leu Gln Arg Ala
 500 505 510

aaa gcg cgg tgg gat ccg cag aac atc ttc cag cac ggc ctg tcg atc 1584
 Lys Ala Arg Trp Asp Pro Gln Asn Ile Phe Gln His Gly Leu Ser Ile
 515 520 525

aaa ccg ccg gca cgg ctt tca ccc ggt cag cca tga 1620
 Lys Pro Pro Ala Arg Leu Ser Pro Gly Gln Pro
 530 535

<210> 16
 <211> 539
 <212> PRT
 <213> Saccharopolyspora spinosa

<400> 16
 Met Ile Ser Ala Ala Gly Glu Gln Ser Gly Pro Val Arg Lys Gly Gly
 1 5 10 15

Ala Val Pro Glu Phe His Asp Pro Ala Pro Met Asn Arg Arg Thr Pro
 20 25 30

Gly Thr Glu Ile Thr Val Glu Pro Asp Asp Pro Arg Tyr Pro Asp Leu
 35 40 45

Val Val Gly His Asn Pro Arg Phe Thr Gly Lys Pro Glu Arg Ile His
 50 55 60

Ile Ala Ser Ser Ala Glu Asp Val Val His Ala Val Ala Asp Ala Val
 65 70 75 80

Arg Thr Gly Arg Arg Val Gly Val Arg Ser Gly Gly His Cys Phe Glu
 85 90 95

Asn Leu Val Ala Asp Pro Ala Ile Arg Val Leu Val Asp Leu Ser Glu
 100 105 110

Leu Asn Arg Val Tyr Tyr Asp Ser Thr Arg Gly Ala Phe Ala Ile Glu
115 120 125

Ala Gly Ala Ala Leu Gly Gln Val Tyr Arg Thr Leu Phe Lys Asn Trp
130 135 140

Gly Val Thr Ile Pro Thr Gly Ala Cys Pro Gly Val Gly Ala Gly Gly
145 150 155 160

His Ile Leu Gly Gly Gly Tyr Gly Pro Leu Ser Arg Arg Phe Gly Ser
165 170 175

Val Val Asp Tyr Leu Gln Gly Val Glu Val Val Val Val Asp Gln Ala
180 185 190

Gly Glu Val His Ile Val Glu Ala Asp Arg Asn Ser Thr Gly Ala Gly
195 200 205

His Asp Leu Trp Trp Ala His Thr Gly Gly Gly Gly Gly Asn Phe Gly
210 215 220

Ile Val Thr Arg Phe Trp Leu Arg Thr Pro Asp Val Val Ser Thr Asp
225 230 235 240

Ala Ala Glu Leu Leu Pro Arg Pro Pro Ala Thr Val Leu Leu Arg Ser
245 250 255

Phe His Trp Pro Trp His Glu Leu Thr Glu Gln Ser Phe Ala Val Leu
260 265 270

Leu Gln Asn Phe Gly Asn Trp Tyr Glu Gln His Ser Ala Pro Glu Ser
275 280 285

Thr Gln Leu Gly Leu Phe Ser Thr Leu Val Cys Ala His Arg Gln Ala
290 295 300

Gly Tyr Val Thr Leu Asn Val His Leu Asp Gly Thr Asp Pro Asn Ala
305 310 315 320

Glu Arg Thr Leu Ala Glu His Leu Ser Ala Ile Asn Ala Gln Val Gly
325 330 335

Val Thr Pro Ala Glu Gly Leu Arg Glu Thr Leu Pro Trp Leu Arg Ser
340 345 350

Thr Gln Val Ala Gly Ala Ile Ala Glu Gly Gly Glu Pro Gly Met Gln
355 360 365

Arg Thr Lys Val Lys Ala Ala Tyr Leu Arg Thr Gly Leu Ser Glu Ala
370 375 380

Gln Leu Ala Thr Val Tyr Arg Arg Leu Thr Val Tyr Gly Tyr Asp Asn
385 390 395 400

Pro Ala Ala Ala Leu Leu Leu Leu Gly Tyr Gly Gly Met Ala Asn Ala
405 410 415

Val Ala Pro Ser Ala Thr Ala Leu Ala Gln Arg Asp Ser Val Leu Lys
420 425 430

Ala Leu Phe Val Thr Asn Trp Ser Glu Pro Ala Glu Asp Glu Arg His
435 440 445

Leu Thr Trp Ile Arg Gly Phe Tyr Arg Glu Met Tyr Ala Glu Thr Gly
450 455 460

Gly Val Pro Val Pro Gly Thr Arg Val Asp Gly Ser Tyr Ile Asn Tyr
465 470 475 480

Pro Asp Thr Asp Leu Ala Asp Pro Leu Trp Asn Thr Ser Gly Val Ala
485 490 495

Trp His Asp Leu Tyr Tyr Lys Asp Asn Tyr Pro Arg Leu Gln Arg Ala
500 505 510

Lys Ala Arg Trp Asp Pro Gln Asn Ile Phe Gln His Gly Leu Ser Ile
515 520 525

Lys Pro Pro Ala Arg Leu Ser Pro Gly Gln Pro
530 535

<210> 17
<211> 1194
<212> DNA
<213> Saccharopolyspora spinosa

<220>

<221> CDS
<222> (1)..(1191)
<223> ORF6; Methyltransferase

<400> 17
atg tcc aca acg cac gag atc gaa acc gtg gaa cgc atc atc ctc gcc 48

Met	Ser	Thr	Thr	His	Glu	Ile	Glu	Thr	Val	Glu	Arg	Ile	Ile	Leu	Ala		
1				5				10					15				
gcc gga tcc agt gcg gcg agc ctg gcc gac ctg acc acc gaa ctc gga																96	
Ala Gly Ser Ser Ala Ala Ser Leu Ala Asp Leu Thr Thr Glu Leu Gly																	
				20					25					30			
ctc gcc agg atc gca ccc gtg ctg atc gac gag atc ctc ttc cgc gcg																144	
Leu Ala Arg Ile Ala Pro Val Leu Ile Asp Glu Ile Leu Phe Arg Ala																	
				35					40					45			
gaa ccg gcc ccc gac atc gaa cgg acc gag gtc gcg gtc cag atc acc																192	
Glu Pro Ala Pro Asp Ile Glu Arg Thr Glu Val Ala Val Gln Ile Thr																	
				50					55					60			
cac cga ggc gag acc gtt gac ttc gtc ctg acg cta cag tcc ggt gag																240	
His Arg Gly Glu Thr Val Asp Phe Val Leu Thr Leu Gln Ser Gly Glu																	
				65					70					75			80
ctg atc aag gcc gag caa cga ccg gtc gga gac gtc ccg ctg cgg atc																288	
Leu Ile Lys Ala Glu Gln Arg Pro Val Gly Asp Val Pro Leu Arg Ile																	
				85					90					95			
ggt tac gag ctc acc gat ctc atc gcc gag ttg ttc ggc cca gga gct																336	
Gly Tyr Glu Leu Thr Asp Leu Ile Ala Glu Leu Phe Gly Pro Gly Ala																	
				100					105					110			
ccc agg gcc gtc ggc gcc cgg agc acc aac ttc ctc cga acc acc aca																384	
Pro Arg Ala Val Gly Ala Arg Ser Thr Asn Phe Leu Arg Thr Thr Thr																	
				115					120					125			
tcc ggt tcg ata ccc ggt ccg tcg gaa ctg tcc gat ggc ttc cag gcc																432	
Ser Gly Ser Ile Pro Gly Pro Ser Glu Leu Ser Asp Gly Phe Gln Ala																	
				130					135					140			
atc tcc gca gtg gtc gcc ggc tgc ggg cac cga cgt ccc gac ctc aac																480	
Ile Ser Ala Val Val Ala Gly Cys Gly His Arg Arg Pro Asp Leu Asn																	
				145					150					155			160
ttg ctc gcc tcc cac tac cgc acg gac aag tgg ggc ggc ctg cac tgg																528	
Leu Leu Ala Ser His Tyr Arg Thr Asp Lys Trp Gly Gly Leu His Trp																	
				165					170					175			
ttc acc ccg cta tac gag cga cac ctc ggc gag ttc cgt gat cgc ccg																576	
Phe Thr Pro Leu Tyr Glu Arg His Leu Gly Glu Phe Arg Asp Arg Pro																	
				180					185					190			
gtg cgc atc ctg gag atc ggt gtc ggt ggc tac aac ttc gac ggt ggc																624	

Val Arg Ile Leu Glu Ile Gly	Val Gly Gly Tyr Asn Phe Asp Gly Gly	
195	200	205
ggc ggc gaa tcc ctg aag atg tgg aag cgc tac ttc cac cgc ggc ctc		672
Gly Gly Glu Ser Leu Lys Met Trp Lys Arg Tyr Phe His Arg Gly Leu		
210	215	220
gtg ttc ggg atg gac gtt ttc gac aag tcc ttc ctc gac cag cag agg		720
Val Phe Gly Met Asp Val Phe Asp Lys Ser Phe Leu Asp Gln Gln Arg		
225	230	235
ctc tgc acc gtc cgc gcc gac cag agc aag ccc gag gag ctg gcc gcc		768
Leu Cys Thr Val Arg Ala Asp Gln Ser Lys Pro Glu Glu Leu Ala Ala		
245	250	255
gtt gac gac aag tac gga ccg ttc gac atc atc atc gac gat ggc agc		816
Val Asp Asp Lys Tyr Gly Pro Phe Asp Ile Ile Ile Asp Asp Gly Ser		
260	265	270
cac atc aac gga cac gtg cgc aca tcc ctg gaa acg ctg ttc ccc cgg		864
His Ile Asn Gly His Val Arg Thr Ser Leu Glu Thr Leu Phe Pro Arg		
275	280	285
ttg cgc agc ggt ggc gta tac gtg atc gag gat ctg tgg acg acc tat		912
Leu Arg Ser Gly Gly Val Tyr Val Ile Glu Asp Leu Trp Thr Thr Tyr		
290	295	300
gct ccc gga ttc ggc ggg cag gcg cag tgc ccg gcc gca ccc ggc acc		960
Ala Pro Gly Phe Gly Gly Gln Ala Gln Cys Pro Ala Ala Pro Gly Thr		
305	310	315
acg gtc agc ctg ctc aag aac ctg ttg gaa ggc gtt cag cac gag gag		1008
Thr Val Ser Leu Leu Lys Asn Leu Leu Glu Gly Val Gln His Glu Glu		
325	330	335
cag ccg cat gcg ggc tcg tac gag ccg agc tac ctg gaa cgc aat ttg		1056
Gln Pro His Ala Gly Ser Tyr Glu Pro Ser Tyr Leu Glu Arg Asn Leu		
340	345	350
gtc ggc ctc cac acc tac cac aac atc gcg ttc ctg gag aaa ggc gtc		1104
Val Gly Leu His Thr Tyr His Asn Ile Ala Phe Leu Glu Lys Gly Val		
355	360	365
aac gcc gaa ggc ggc gtt cct gct tgg gtg cca agg agt ctg gac gac		1152
Asn Ala Glu Gly Gly Val Pro Ala Trp Val Pro Arg Ser Leu Asp Asp		
370	375	380
ata ttg cac ctg gcc gac gtg aac agc gcg gag gac gag tga		1194

Ile Leu His Leu Asp Val Asn Ser Ala Glu Asp Glu
385 390 395

<210> 18

<211> 397

<212> PRT

<213> Saccharopolyspora spinosa

<400> 18

Met Ser Thr Thr His Glu Ile Glu Thr Val Glu Arg Ile Ile Leu Ala
1 5 10 15

Ala Gly Ser Ser Ala Ala Ser Leu Ala Asp Leu Thr Thr Glu Leu Gly
20 25 30

Leu Ala Arg Ile Ala Pro Val Leu Ile Asp Glu Ile Leu Phe Arg Ala
35 40 45

Glu Pro Ala Pro Asp Ile Glu Arg Thr Glu Val Ala Val Gln Ile Thr
50 55 60

His Arg Gly Glu Thr Val Asp Phe Val Leu Thr Leu Gln Ser Gly Glu
65 70 75 80

Leu Ile Lys Ala Glu Gln Arg Pro Val Gly Asp Val Pro Leu Arg Ile
85 90 95

Gly Tyr Glu Leu Thr Asp Leu Ile Ala Glu Leu Phe Gly Pro Gly Ala
100 105 110

Pro Arg Ala Val Gly Ala Arg Ser Thr Asn Phe Leu Arg Thr Thr Thr
115 120 125

Ser Gly Ser Ile Pro Gly Pro Ser Glu Leu Ser Asp Gly Phe Gln Ala
130 135 140

Ile Ser Ala Val Val Ala Gly Cys Gly His Arg Arg Pro Asp Leu Asn
145 150 155 160

Leu Leu Ala Ser His Tyr Arg Thr Asp Lys Trp Gly Gly Leu His Trp
165 170 175

Phe Thr Pro Leu Tyr Glu Arg His Leu Gly Glu Phe Arg Asp Arg Pro
180 185 190

Val Arg Ile Leu Glu Ile Gly Val Gly Gly Tyr Asn Phe Asp Gly Gly
195 200 205

Gly Gly Glu Ser Leu Lys Met Trp Lys Arg Tyr Phe His Arg Gly Leu
210 215 220

Val Phe Gly Met Asp Val Phe Asp Lys Ser Phe Leu Asp Gln Gln Arg
225 230 235 240

Leu Cys Thr Val Arg Ala Asp Gln Ser Lys Pro Glu Glu Leu Ala Ala
245 250 255

Val Asp Asp Lys Tyr Gly Pro Phe Asp Ile Ile Ile Asp Asp Gly Ser
260 265 270

His Ile Asn Gly His Val Arg Thr Ser Leu Glu Thr Leu Phe Pro Arg
275 280 285

Leu Arg Ser Gly Gly Val Tyr Val Ile Glu Asp Leu Trp Thr Thr Tyr
290 295 300

Ala Pro Gly Phe Gly Gly Gln Ala Gln Cys Pro Ala Ala Pro Gly Thr
305 310 315 320

Thr Val Ser Leu Leu Lys Asn Leu Leu Glu Gly Val Gln His Glu Glu
325 330 335

Gln Pro His Ala Gly Ser Tyr Glu Pro Ser Tyr Leu Glu Arg Asn Leu
340 345 350

Val Gly Leu His Thr Tyr His Asn Ile Ala Phe Leu Glu Lys Gly Val
355 360 365

Asn Ala Glu Gly Gly Val Pro Ala Trp Val Pro Arg Ser Leu Asp Asp
370 375 380

Ile Leu His Leu Ala Asp Val Asn Ser Ala Glu Asp Glu
385 390 395

<210> 19

<211> 900

<212> DNA

<213> *Saccharopolyspora spinosa*

<220>

<221> CDS

<222> (1)..(897)

<223> ORF7; O-Methyltransferase

<400> 19

gtg aac agc aga ggg gcg aac aca cag gca ttt ccg acc gcg gat cag 48
Val Asn Ser Arg Gly Ala Asn Thr Gln Ala Phe Pro Thr Ala Asp Gln
1 5 10 15

gtg gag tcc atc ttc gat gcg ttg gcg cac ggg cgt ccc ctg cac cac 96
Val Glu Ser Ile Phe Asp Ala Leu Ala His Gly Arg Pro Leu His His
20 25 30

ggt tac tgg gcg ggc ggg tat cgg gag gat gcc ggt gcc aca ccg tgg 144
Gly Tyr Trp Ala Gly Gly Tyr Arg Glu Asp Ala Gly Ala Thr Pro Trp
35 40 45

tcg gat gct gcc gac caa ctg acc gac ctg ttc atc gac aag gcc gcg 192
Ser Asp Ala Ala Asp Gln Leu Thr Asp Leu Phe Ile Asp Lys Ala Ala
50 55 60

ctc cgt ccc gga gcg cac ctg ttc gac ctg ggc tgc ggc aat ggg cag 240
Leu Arg Pro Gly Ala His Leu Phe Asp Leu Gly Cys Gly Asn Gly Gln
65 70 75 80

ccc gta gtc cgt gcg gca tgc gcc agc ggc gtt cga gtc acc gga atc 288
Pro Val Val Arg Ala Ala Cys Ala Ser Gly Val Arg Val Thr Gly Ile
85 90 95

acc gtg aac gcc cag cat ctc gcc gcc gcc acc agg ctc gcc aac gag 336
Thr Val Asn Ala Gln His Leu Ala Ala Ala Thr Arg Leu Ala Asn Glu
100 105 110

acc gga ctg gcc ggc agt ctt gag ttc gat cta gtc gac ggc gcc cag 384
Thr Gly Leu Ala Gly Ser Leu Glu Phe Asp Leu Val Asp Gly Ala Gln
115 120 125

ctg ccc tac ccg gac ggt ttc ttt cag gcc gca tgg gcg atg cag tcc 432
Leu Pro Tyr Pro Asp Gly Phe Phe Gln Ala Ala Trp Ala Met Gln Ser
130 135 140

gtc gtg cag atc gtg gac cag gcc gcc gcg atc cgc gag gtc cac cga 480
Val Val Gln Ile Val Asp Gln Ala Ala Ala Ile Arg Glu Val His Arg
145 150 155 160

atc ctg gaa ccc ggc ggc cgg ttc gtc ctc gga gac atc atc act cgg 528
Ile Leu Glu Pro Gly Gly Arg Phe Val Leu Gly Asp Ile Ile Thr Arg
165 170 175

gtt cga ctc ccg gaa gag tac gcg gcg gtt tgg acg ggc acg acc gcc 576
Val Arg Leu Pro Glu Glu Tyr Ala Ala Val Trp Thr Gly Thr Thr Ala

180

185

190

cat acc ttg aac agc ttc acg gcg ctg gtc agc gaa gcc ggg ttc gag 624
 His Thr Leu Asn Ser Phe Thr Ala Leu Val Ser Glu Ala Gly Phe Glu
 195 200 205

att ctc gaa gtc acc gac ctc acg gca cag acc agg tgc atg gtc tcc 672
 Ile Leu Glu Val Thr Asp Leu Thr Ala Gln Thr Arg Cys Met Val Ser
 210 215 220

tgg tac gtc gac gag ttg ctc cgg aaa ctc gat gag ctc gcc ggc gtc 720
 Trp Tyr Val Asp Glu Leu Leu Arg Lys Leu Asp Glu Leu Ala Gly Val
 225 230 235 240

gag cct gcg gct gtc ggc acc tac cag caa cgc tac ttg gga gac atc 768
 Glu Pro Ala Ala Val Gly Thr Tyr Gln Gln Arg Tyr Leu Gly Asp Ile
 245 250 255

gcg gcg aag cac gga ccg gga cca gca cag ctg atc gcc gcg gtt gcg 816
 Ala Ala Lys His Gly Pro Gly Pro Ala Gln Leu Ile Ala Ala Val Ala
 260 265 270

gaa tac cgg aaa cat ccg gat tac gcc aga aac gag gaa agc atg ggt 864
 Glu Tyr Arg Lys His Pro Asp Tyr Ala Arg Asn Glu Glu Ser Met Gly
 275 280 285

ttc atg ctc ctg cag gct cga aag aag cag tcc tga 900
 Phe Met Leu Leu Gln Ala Arg Lys Lys Gln Ser
 290 295

<210> 20

<211> 299

<212> PRT

<213> Saccharopolyspora spinosa

<400> 20

Val Asn Ser Arg Gly Ala Asn Thr Gln Ala Phe Pro Thr Ala Asp Gln
 1 5 10 15

Val Glu Ser Ile Phe Asp Ala Leu Ala His Gly Arg Pro Leu His His
 20 25 30

Gly Tyr Trp Ala Gly Gly Tyr Arg Glu Asp Ala Gly Ala Thr Pro Trp
 35 40 45

Ser Asp Ala Ala Asp Gln Leu Thr Asp Leu Phe Ile Asp Lys Ala Ala
 50 55 60

Leu Arg Pro Gly Ala His Leu Phe Asp Leu Gly Cys Gly Asn Gly Gln
65 70 75 80

Pro Val Val Arg Ala Ala Cys Ala Ser Gly Val Arg Val Thr Gly Ile
85 90 95

Thr Val Asn Ala Gln His Leu Ala Ala Ala Thr Arg Leu Ala Asn Glu
100 105 110

Thr Gly Leu Ala Gly Ser Leu Glu Phe Asp Leu Val Asp Gly Ala Gln
115 120 125

Leu Pro Tyr Pro Asp Gly Phe Phe Gln Ala Ala Trp Ala Met Gln Ser
130 135 140

Val Val Gln Ile Val Asp Gln Ala Ala Ala Ile Arg Glu Val His Arg
145 150 155 160

Ile Leu Glu Pro Gly Gly Arg Phe Val Leu Gly Asp Ile Ile Thr Arg
165 170 175

Val Arg Leu Pro Glu Glu Tyr Ala Ala Val Trp Thr Gly Thr Thr Ala
180 185 190

His Thr Leu Asn Ser Phe Thr Ala Leu Val Ser Glu Ala Gly Phe Glu
195 200 205

Ile Leu Glu Val Thr Asp Leu Thr Ala Gln Thr Arg Cys Met Val Ser
210 215 220

Trp Tyr Val Asp Glu Leu Leu Arg Lys Leu Asp Glu Leu Ala Gly Val
225 230 235 240

Glu Pro Ala Ala Val Gly Thr Tyr Gln Gln Arg Tyr Leu Gly Asp Ile
245 250 255

Ala Ala Lys His Gly Pro Gly Pro Ala Gln Leu Ile Ala Ala Val Ala
260 265 270

Glu Tyr Arg Lys His Pro Asp Tyr Ala Arg Asn Glu Glu Ser Met Gly
275 280 285

Phe Met Leu Leu Gln Ala Arg Lys Lys Gln Ser
290 295

<210> 21
 <211> 1167
 <212> DNA
 <213> Saccharopolyspora spinosa

<220>
 <221> CDS
 <222> (1)..(1164)
 <223> ORF8; Cyclisierungsenzym

<400> 21

atg gcc tcc gag cac gcc agc ctg gtc ggc gac gat ctg cgg gca ccc 48
 Met Ala Ser Glu His Ala Ser Leu Val Gly Asp Asp Leu Arg Ala Pro
 1 5 10 15

gcg gat gat ccc ttc tac cga ccg ccg acg ccg cta ccg ccg ggt gtc 96
 Ala Asp Asp Pro Phe Tyr Arg Pro Pro Thr Pro Leu Pro Pro Gly Val
 20 25 30

ccg ggc acg ctc ctc agg gcc cgg ccc gtc tcg gca ctg cgc ggc acg 144
 Pro Gly Thr Leu Leu Arg Ala Arg Pro Val Ser Ala Leu Arg Gly Thr
 35 40 45

ggc gaa ccc gtc gca gcc aag gcc tgg caa atc ctc tac cgg tcc aac 192
 Gly Glu Pro Val Ala Ala Lys Ala Trp Gln Ile Leu Tyr Arg Ser Asn
 50 55 60

tcc gcc ctt ggc atg ccg aac gcc gtc tcc ggc acc gtt ctg gtg ccg 240
 Ser Ala Leu Gly Met Pro Asn Ala Val Ser Gly Thr Val Leu Val Pro
 65 70 75 80

aac atc ccg tgg ccg cgc gaa gat cgc ccc atc atc act ttc gca gtg 288
 Asn Ile Pro Trp Pro Arg Glu Asp Arg Pro Ile Ile Thr Phe Ala Val
 85 90 95

ggc acc cac ggc ctc ggt agc caa gtt gcc ccg tcg tac ctg ctt cga 336
 Gly Thr His Gly Leu Gly Ser Gln Val Ala Pro Ser Tyr Leu Leu Arg
 100 105 110

acc gga acc gag ccg gag acc gag ctg atc gcc gtg gcc ctc gac cgc 384
 Thr Gly Thr Glu Pro Glu Thr Glu Leu Ile Ala Val Ala Leu Asp Arg
 115 120 125

ggg tgg gcc gtg gtc atc acc gac tac gaa ggc ctc ggt act cct gga 432
 Gly Trp Ala Val Val Ile Thr Asp Tyr Glu Gly Leu Gly Thr Pro Gly
 130 135 140

acc cac acc tac acc gtc ggc agg gcg cag gga cac gcc atg ctc gat 480

Thr His Thr Tyr Thr Val Gly Arg Ala Gln Gly His Ala Met Leu Asp
 145 150 155 160

gcc gcc cgc gct gcg caa cgg cta ccg ggc tcc ggc ctg acg acc gac 528
 Ala Ala Arg Ala Ala Gln Arg Leu Pro Gly Ser Gly Leu Thr Thr Asp
 165 170 175

tgc ccg gtc ggc atc tgg ggc tat gcg cag ggt ggg caa gcg tcg gcc 576
 Cys Pro Val Gly Ile Trp Gly Tyr Ala Gln Gly Gly Gln Ala Ser Ala
 180 185 190

ttc gcc ggc gaa ctg cac ccc acc tac gca cct gaa ctg cga atc cgc 624
 Phe Ala Gly Glu Leu His Pro Thr Tyr Ala Pro Glu Leu Arg Ile Arg
 195 200 205

gct gcg gcc gca ggt gcg gtg ccg atc gat ctg ctg gac atc atc cac 672
 Ala Ala Ala Ala Gly Ala Val Pro Ile Asp Leu Leu Asp Ile Ile His
 210 215 220

cga aat gac ggg gtg ttc acc ggg ccg gtg ctg gcc ggc ctg gtc ggg 720
 Arg Asn Asp Gly Val Phe Thr Gly Pro Val Leu Ala Gly Leu Val Gly
 225 230 235 240

cat gcc gct gcc tac ccc gat ctg cca ttc gac gag ctt ctc acc gaa 768
 His Ala Ala Ala Tyr Pro Asp Leu Pro Phe Asp Glu Leu Leu Thr Glu
 245 250 255

gcg ggt cgt acc gcc gtt gat caa gtg cgc gag ctc ggt gca ccg gag 816
 Ala Gly Arg Thr Ala Val Asp Gln Val Arg Glu Leu Gly Ala Pro Glu
 260 265 270

ctc gtc acc cgc ttc ctc ggc cgc gag ctg agc gac ttc ctc gac act 864
 Leu Val Thr Arg Phe Leu Gly Arg Glu Leu Ser Asp Phe Leu Asp Thr
 275 280 285

tcc ggc ctt ttc gag caa cct cga tgg cgc gca cga ctg gcc gaa agc 912
 Ser Gly Leu Phe Glu Gln Pro Arg Trp Arg Ala Arg Leu Ala Glu Ser
 290 295 300

gtc gca ggt agg aac ggt ggc ccg gtg gtc ccc acg ctc gtc tac cac 960
 Val Ala Gly Arg Asn Gly Gly Pro Val Val Pro Thr Leu Val Tyr His
 305 310 315 320

agc acg gac gac gag atc gtt ccg ttc gca ttc ggc gag cga ctc cgg 1008
 Ser Thr Asp Asp Glu Ile Val Pro Phe Ala Phe Gly Glu Arg Leu Arg
 325 330 335

gac agc tac cgc gcg gcg ggt acg cca gtg cgg tgg cat ccg ctc tcc 1056

Asp Ser Tyr Arg Ala Ala Gly Thr Pro Val Arg Trp His Pro Leu Ser
 340 345 350

gga ttg gct cac ttt ccc gcc gcc ctg gcc agc tcg cga gtg gtc gtc 1104
 Gly Leu Ala His Phe Pro Ala Ala Leu Ala Ser Ser Arg Val Val Val
 355 360 365

tcg tgg ttc gac gag cac ttc tcc gag ccg tcc gcg atc agc ggt ccg 1152
 Ser Trp Phe Asp Glu His Phe Ser Glu Pro Ser Ala Ile Ser Gly Pro
 370 375 380

cga gat gcc agg tga 1167
 Arg Asp Ala Arg
 385

<210> 22
 <211> 388
 <212> PRT
 <213> Saccharopolyspora spinosa

<400> 22
 Met Ala Ser Glu His Ala Ser Leu Val Gly Asp Asp Leu Arg Ala Pro
 1 5 10 15

Ala Asp Asp Pro Phe Tyr Arg Pro Pro Thr Pro Leu Pro Pro Gly Val
 20 25 30

Pro Gly Thr Leu Leu Arg Ala Arg Pro Val Ser Ala Leu Arg Gly Thr
 35 40 45

Gly Glu Pro Val Ala Ala Lys Ala Trp Gln Ile Leu Tyr Arg Ser Asn
 50 55 60

Ser Ala Leu Gly Met Pro Asn Ala Val Ser Gly Thr Val Leu Val Pro
 65 70 75 80

Asn Ile Pro Trp Pro Arg Glu Asp Arg Pro Ile Ile Thr Phe Ala Val
 85 90 95

Gly Thr His Gly Leu Gly Ser Gln Val Ala Pro Ser Tyr Leu Leu Arg
 100 105 110

Thr Gly Thr Glu Pro Glu Thr Glu Leu Ile Ala Val Ala Leu Asp Arg
 115 120 125

Gly Trp Ala Val Val Ile Thr Asp Tyr Glu Gly Leu Gly Thr Pro Gly
 130 135 140

Thr His Thr Tyr Thr Val Gly Arg Ala Gln Gly His Ala Met Leu Asp
145 150 155 160

Ala Ala Arg Ala Ala Gln Arg Leu Pro Gly Ser Gly Leu Thr Thr Asp
165 170 175

Cys Pro Val Gly Ile Trp Gly Tyr Ala Gln Gly Gly Gln Ala Ser Ala
180 185 190

Phe Ala Gly Glu Leu His Pro Thr Tyr Ala Pro Glu Leu Arg Ile Arg
195 200 205

Ala Ala Ala Ala Gly Ala Val Pro Ile Asp Leu Leu Asp Ile Ile His
210 215 220

Arg Asn Asp Gly Val Phe Thr Gly Pro Val Leu Ala Gly Leu Val Gly
225 230 235 240

His Ala Ala Ala Tyr Pro Asp Leu Pro Phe Asp Glu Leu Leu Thr Glu
245 250 255

Ala Gly Arg Thr Ala Val Asp Gln Val Arg Glu Leu Gly Ala Pro Glu
260 265 270

Leu Val Thr Arg Phe Leu Gly Arg Glu Leu Ser Asp Phe Leu Asp Thr
275 280 285

Ser Gly Leu Phe Glu Gln Pro Arg Trp Arg Ala Arg Leu Ala Glu Ser
290 295 300

Val Ala Gly Arg Asn Gly Gly Pro Val Val Pro Thr Leu Val Tyr His
305 310 315 320

Ser Thr Asp Asp Glu Ile Val Pro Phe Ala Phe Gly Glu Arg Leu Arg
325 330 335

Asp Ser Tyr Arg Ala Ala Gly Thr Pro Val Arg Trp His Pro Leu Ser
340 345 350

Gly Leu Ala His Phe Pro Ala Ala Leu Ala Ser Ser Arg Val Val Val
355 360 365

Ser Trp Phe Asp Glu His Phe Ser Glu Pro Ser Ala Ile Ser Gly Pro
370 375 380

Arg Asp Ala Arg
385

<210> 23
 <211> 1011
 <212> DNA
 <213> Saccharopolyspora spinosa

<220>
 <221> CDS
 <222> (1)..(1008)
 <223> ORF9; 2,3-Reduktase

<400> 23
 atg acc agc tcg atg cga aag ccg gtg cgc atc ggt gtg ctc ggg tgc 48
 Met Thr Ser Ser Met Arg Lys Pro Val Arg Ile Gly Val Leu Gly Cys
 1 5 10 15
 gct tcc ttc gcg tgg cga cgg atg ctg ccc gcg atg tgc gac gtg gcc 96
 Ala Ser Phe Ala Trp Arg Arg Met Leu Pro Ala Met Cys Asp Val Ala
 20 25 30
 gaa aca gag gtg gtg gcg gtg gcg agc cgt gat ccg gcg aaa gcc gaa 144
 Glu Thr Glu Val Val Ala Val Ala Ser Arg Asp Pro Ala Lys Ala Glu
 35 40 45
 cgg ttc gca gcg cga ttc gaa tgc gag gcg gtg ctg ggt tac cag cgg 192
 Arg Phe Ala Ala Arg Phe Glu Cys Glu Ala Val Leu Gly Tyr Gln Arg
 50 55 60
 ctc ctg gag cgg ccg gac atc gat gcc gtc tac gtg ccg ttg ccg cct 240
 Leu Leu Glu Arg Pro Asp Ile Asp Ala Val Tyr Val Pro Leu Pro Pro
 65 70 75 80
 ggc atg cat gca gag tgg atc ggc aag gcg ctt gag gca gac aaa cac 288
 Gly Met His Ala Glu Trp Ile Gly Lys Ala Leu Glu Ala Asp Lys His
 85 90 95
 gtg ctt gcg gag aaa ccg ctg acg acg acg gcg tcc gac acc gct cgc 336
 Val Leu Ala Glu Lys Pro Leu Thr Thr Thr Ala Ser Asp Thr Ala Arg
 100 105 110

ctg gtc ggg ctg gcc agg agg aag aac ctg ctg ctg cgg gag aat tac 384
 Leu Val Gly Leu Ala Arg Arg Lys Asn Leu Leu Leu Arg Glu Asn Tyr
 115 120 125

ctg ttc ctc cac cac ggc cgg cac gac gtg gtc cgc gac ctg ctg caa 432
 Leu Phe Leu His His Gly Arg His Asp Val Val Arg Asp Leu Leu Gln

130

135

140

tcc ggg gag atc ggt gag ctc cgg gag ttc acc gcc gtg ttc gga att 480
 Ser Gly Glu Ile Gly Glu Leu Arg Glu Phe Thr Ala Val Phe Gly Ile
 145 150 155 160

ccg ccg ctt ccc gac acg gac atc cgc tat cgc acc gaa ctc ggt ggc 528
 Pro Pro Leu Pro Asp Thr Asp Ile Arg Tyr Arg Thr Glu Leu Gly Gly
 165 170 175

gga gcg ttg ctg gac atc ggt gtc tat ccc gcc cgt gcc gct cgg cac 576
 Gly Ala Leu Leu Asp Ile Gly Val Tyr Pro Ala Arg Ala Ala Arg His
 180 185 190

ttt ctc ctc ggt ccg ctc acg gtt ctc ggc gca agc tcg cac gag gcc 624
 Phe Leu Leu Gly Pro Leu Thr Val Leu Gly Ala Ser Ser His Glu Ala
 195 200 205

cag gag tcg ggc gtc gac ttg tcg ggc agc gtg ctg ctc caa tcg gaa 672
 Gln Glu Ser Gly Val Asp Leu Ser Gly Ser Val Leu Leu Gln Ser Glu
 210 215 220

ggt ggc acc gtt gcc cac ctc gga tac ggt ttc gtg cac cac tac cgc 720
 Gly Gly Thr Val Ala His Leu Gly Tyr Gly Phe Val His His Tyr Arg
 225 230 235 240

agc gcg tac gag ctg tgg ggg agt cgt ggg cga atc gtc gtc gac cgg 768
 Ser Ala Tyr Glu Leu Trp Gly Ser Arg Gly Arg Ile Val Val Asp Arg
 245 250 255

gcg ttc acg ccg ccc gcc gag tgg cag gcc gtg atc cga atc gag cgg 816
 Ala Phe Thr Pro Pro Ala Glu Trp Gln Ala Val Ile Arg Ile Glu Arg
 260 265 270

aag ggc gtt gtc gac gag ttg tcc ttg cca gcg gaa gat cag gtt cgc 864
 Lys Gly Val Val Asp Glu Leu Ser Leu Pro Ala Glu Asp Gln Val Arg
 275 280 285

aag gcg gtc acc gcc ttc gca cgc gac atc aga gca ggg aca ggc gtg 912
 Lys Ala Val Thr Ala Phe Ala Arg Asp Ile Arg Ala Gly Thr Gly Val
 290 295 300

gac gac cct gcg gtg gcc gga gat tcg ggc gaa tcg atg atc cag cag 960
 Asp Asp Pro Ala Val Ala Gly Asp Ser Gly Glu Ser Met Ile Gln Gln
 305 310 315 320

gcc gcg ctg gtg gag gcg atc ggt cag gcc cgt cgg tgc ggg tcc aca 1008
 Ala Ala Leu Val Glu Ala Ile Gly Gln Ala Arg Arg Cys Gly Ser Thr

325

330

335

tag

1011

<210> 24

<211> 336

<212> PRT

<213> Saccharopolyspora spinosa

<400> 24

Met Thr Ser Ser Met Arg Lys Pro Val Arg Ile Gly Val Leu Gly Cys

1

5

10

15

Ala Ser Phe Ala Trp Arg Arg Met Leu Pro Ala Met Cys Asp Val Ala

20

25

30

Glu Thr Glu Val Val Ala Val Ala Ser Arg Asp Pro Ala Lys Ala Glu

35

40

45

Arg Phe Ala Ala Arg Phe Glu Cys Glu Ala Val Leu Gly Tyr Gln Arg

50

55

60

Leu Leu Glu Arg Pro Asp Ile Asp Ala Val Tyr Val Pro Leu Pro Pro

65

70

75

80

Gly Met His Ala Glu Trp Ile Gly Lys Ala Leu Glu Ala Asp Lys His

85

90

95

Val Leu Ala Glu Lys Pro Leu Thr Thr Thr Ala Ser Asp Thr Ala Arg

100

105

110

Leu Val Gly Leu Ala Arg Arg Lys Asn Leu Leu Leu Arg Glu Asn Tyr

115

120

125

Leu Phe Leu His His Gly Arg His Asp Val Val Arg Asp Leu Leu Gln

130

135

140

Ser Gly Glu Ile Gly Glu Leu Arg Glu Phe Thr Ala Val Phe Gly Ile

145

150

155

160

Pro Pro Leu Pro Asp Thr Asp Ile Arg Tyr Arg Thr Glu Leu Gly Gly

165

170

175

Gly Ala Leu Leu Asp Ile Gly Val Tyr Pro Ala Arg Ala Ala Arg His

180

185

190

Phe Leu Leu Gly Pro Leu Thr Val Leu Gly Ala Ser Ser His Glu Ala

195

200

205

Gln Glu Ser Gly Val Asp Leu Ser Gly Ser Val Leu Leu Gln Ser Glu
 210 215 220

Gly Gly Thr Val Ala His Leu Gly Tyr Gly Phe Val His His Tyr Arg
 225 230 235 240

Ser Ala Tyr Glu Leu Trp Gly Ser Arg Gly Arg Ile Val Val Asp Arg
 245 250 255

Ala Phe Thr Pro Pro Ala Glu Trp Gln Ala Val Ile Arg Ile Glu Arg
 260 265 270

Lys Gly Val Val Asp Glu Leu Ser Leu Pro Ala Glu Asp Gln Val Arg
 275 280 285

Lys Ala Val Thr Ala Phe Ala Arg Asp Ile Arg Ala Gly Thr Gly Val
 290 295 300

Asp Asp Pro Ala Val Ala Gly Asp Ser Gly Glu Ser Met Ile Gln Gln
 305 310 315 320

Ala Ala Leu Val Glu Ala Ile Gly Gln Ala Arg Arg Cys Gly Ser Thr
 325 330 335

<210> 25

<211> 1461

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1458)

<223> ORF10; 2,3-Dehydratase

<400> 25

atg agc agt tct gtc gaa gct gag gca agt gct gct gcg ccg ctc ggc 48
 Met Ser Ser Ser Val Glu Ala Glu Ala Ser Ala Ala Ala Pro Leu Gly
 1 5 10 15

agc aac aac acg cgg cgg ttc gtc gac tct gcg ctg agc gct tgc aat 96
 Ser Asn Asn Thr Arg Arg Phe Val Asp Ser Ala Leu Ser Ala Cys Asn
 20 25 30

ggc atg att ccg acc acg gag ttc cac tgc tgg ctc gcc gat cgg ctg 144

Gly	Met	Ile	Pro	Thr	Thr	Glu	Phe	His	Cys	Trp	Leu	Ala	Asp	Arg	Leu	
		35					40					45				
ggc	gag	aac	agc	ttc	gag	acc	aat	cgc	atc	ccg	ttc	gac	cgc	ctg	tcg	192
Gly	Glu	Asn	Ser	Phe	Glu	Thr	Asn	Arg	Ile	Pro	Phe	Asp	Arg	Leu	Ser	
	50					55				60						
aaa	tgg	aaa	ttc	gat	gcc	agc	acg	gag	aac	ctg	gtt	cat	gcc	gac	ggt	240
Lys	Trp	Lys	Phe	Asp	Ala	Ser	Thr	Glu	Asn	Leu	Val	His	Ala	Asp	Gly	
	65				70				75						80	
agg	ttc	ttc	acg	gta	gaa	ggc	ctg	cag	gtc	gag	acc	aac	tat	ggc	gcg	288
Arg	Phe	Phe	Thr	Val	Glu	Gly	Leu	Gln	Val	Glu	Thr	Asn	Tyr	Gly	Ala	
			85					90					95			
gca	ccc	agc	tgg	cac	cag	ccg	atc	atc	aac	cag	gct	gaa	gta	ggt	atc	336
Ala	Pro	Ser	Trp	His	Gln	Pro	Ile	Ile	Asn	Gln	Ala	Glu	Val	Gly	Ile	
			100				105					110				
ctc	ggc	att	ctc	gtc	aag	gag	atc	gac	ggc	gtg	ctg	cac	tgc	ctc	atg	384
Leu	Gly	Ile	Leu	Val	Lys	Glu	Ile	Asp	Gly	Val	Leu	His	Cys	Leu	Met	
		115					120					125				
tca	gca	aag	atg	gaa	ccg	ggc	aac	gtc	aac	gtc	ctg	cag	ctc	tcg	ccg	432
Ser	Ala	Lys	Met	Glu	Pro	Gly	Asn	Val	Asn	Val	Leu	Gln	Leu	Ser	Pro	
	130					135					140					
acg	gtt	cag	gca	act	cgg	agc	aac	tac	acg	cag	gca	cac	cgt	ggc	agc	480
Thr	Val	Gln	Ala	Thr	Arg	Ser	Asn	Tyr	Thr	Gln	Ala	His	Arg	Gly	Ser	
	145				150				155					160		
gtt	ccg	ccc	tat	gtg	gac	tac	ttc	ctc	ggg	cgg	ggc	cgc	ggc	cgc	gtg	528
Val	Pro	Pro	Tyr	Val	Asp	Tyr	Phe	Leu	Gly	Arg	Gly	Arg	Gly	Arg	Val	
			165					170				175				
ctg	gta	gac	gtg	ctc	cag	tct	gaa	cag	ggg	tcc	tgg	ttc	tac	cgg	aag	576
Leu	Val	Asp	Val	Leu	Gln	Ser	Glu	Gln	Gly	Ser	Trp	Phe	Tyr	Arg	Lys	
			180					185				190				
cgc	aac	cgg	aac	atg	gtg	gtg	gaa	gtc	cag	gag	gaa	gtg	cca	gtc	ctg	624
Arg	Asn	Arg	Asn	Met	Val	Val	Glu	Val	Gln	Glu	Glu	Val	Pro	Val	Leu	
	195						200					205				
cca	gac	ttc	tgc	tgg	ttg	acg	ctc	ggc	cag	gtg	ctg	gct	ctc	ctt	cgt	672
Pro	Asp	Phe	Cys	Trp	Leu	Thr	Leu	Gly	Gln	Val	Leu	Ala	Leu	Leu	Arg	
	210					215					220					
cag	gac	aac	atc	gtc	aac	atg	gac	acc	cgg	acg	gtg	ctg	tct	tgc	atc	720

Gln Asp Asn Ile Val Asn Met Asp Thr Arg Thr Val Leu Ser Cys Ile
 225 230 235 240

ccg ttc cac gat tcc gcc acc gga ccc gaa cta gcc gcc tcg gag gag 768
 Pro Phe His Asp Ser Ala Thr Gly Pro Glu Leu Ala Ala Ser Glu Glu
 245 250 255

ccc ttc cga cag gcg gtg gcc agg tcg ctc tcg cac ggc atc gat tcg 816
 Pro Phe Arg Gln Ala Val Ala Arg Ser Leu Ser His Gly Ile Asp Ser
 260 265 270

tcg agt atc tcc gag gcg gtc ggt tgg ttc gag gaa gcc aag gcc cgc 864
 Ser Ser Ile Ser Glu Ala Val Gly Trp Phe Glu Glu Ala Lys Ala Arg
 275 280 285

tac cgc ttg cgg gca acg cgc gtt ccg ctg agc agg gtc gac aag tgg 912
 Tyr Arg Leu Arg Ala Thr Arg Val Pro Leu Ser Arg Val Asp Lys Trp
 290 295 300

tat cgc acc gat acc gag atc gcc cac cag gac ggc aag tac ttc gcg 960
 Tyr Arg Thr Asp Thr Glu Ile Ala His Gln Asp Gly Lys Tyr Phe Ala
 305 310 315 320

gtg atc gcg gtg tcg gtg tcc gcg acc aat cgt gag gtc gcc agc tgg 1008
 Val Ile Ala Val Ser Val Ser Ala Thr Asn Arg Glu Val Ala Ser Trp
 325 330 335

acg cag ccg atg atc gaa ccg cga gaa caa ggt gag atc gca ctg ttg 1056
 Thr Gln Pro Met Ile Glu Pro Arg Glu Gln Gly Glu Ile Ala Leu Leu
 340 345 350

gtc aag cgg atc ggc gga gtg ctg cac ggt ttg gtc cac gct cgg gtg 1104
 Val Lys Arg Ile Gly Gly Val Leu His Gly Leu Val His Ala Arg Val
 355 360 365

gag gct ggg tat aag tgg act gcg gaa atc gct ccc acg gtc cag tgc 1152
 Glu Ala Gly Tyr Lys Trp Thr Ala Glu Ile Ala Pro Thr Val Gln Cys
 370 375 380

agt gtg gcc aac tac caa agc acc ccg tcg aac gac tgg ccg ccg ttc 1200
 Ser Val Ala Asn Tyr Gln Ser Thr Pro Ser Asn Asp Trp Pro Pro Phe
 385 390 395 400

ttg gac gac gtg ctc acc gcc gat ccc gaa acc gtg cgg tac gaa tcg 1248
 Leu Asp Asp Val Leu Thr Ala Asp Pro Glu Thr Val Arg Tyr Glu Ser
 405 410 415

atc ctg tcc gaa gaa ggc ggt cgg ttc tac cag gcg cag aac agg tac 1296

Ile Leu Ser Glu Glu Gly Gly Arg Phe Tyr Gln Ala Gln Asn Arg Tyr
 420 425 430

cgg atc atc gag gtg cat gag gac ttc gcg gca cga cct ccc agc gac 1344
 Arg Ile Ile Glu Val His Glu Asp Phe Ala Ala Arg Pro Pro Ser Asp
 435 440 445

ttc cgg tgg atg act ttg gga cag ttg ggc gag ctg ctc cgg agc acc 1392
 Phe Arg Trp Met Thr Leu Gly Gln Leu Gly Glu Leu Leu Arg Ser Thr
 450 455 460

cac ttc ttg aac atc cag gcg cgc agc ttg gtc gcc tcc ctg cat agc 1440
 His Phe Leu Asn Ile Gln Ala Arg Ser Leu Val Ala Ser Leu His Ser
 465 470 475 480

ttg tgg gcg ttg ggg cga tga 1461
 Leu Trp Ala Leu Gly Arg
 485

<210> 26
 <211> 486
 <212> PRT
 <213> Saccharopolyspora spinosa

<400> 26
 Met Ser Ser Ser Val Glu Ala Glu Ala Ser Ala Ala Ala Pro Leu Gly
 1 5 10 15

Ser Asn Asn Thr Arg Arg Phe Val Asp Ser Ala Leu Ser Ala Cys Asn
 20 25 30

Gly Met Ile Pro Thr Thr Glu Phe His Cys Trp Leu Ala Asp Arg Leu
 35 40 45

Gly Glu Asn Ser Phe Glu Thr Asn Arg Ile Pro Phe Asp Arg Leu Ser
 50 55 60

Lys Trp Lys Phe Asp Ala Ser Thr Glu Asn Leu Val His Ala Asp Gly
 65 70 75 80

Arg Phe Phe Thr Val Glu Gly Leu Gln Val Glu Thr Asn Tyr Gly Ala
 85 90 95

Ala Pro Ser Trp His Gln Pro Ile Ile Asn Gln Ala Glu Val Gly Ile
 100 105 110

Leu Gly Ile Leu Val Lys Glu Ile Asp Gly Val Leu His Cys Leu Met

115

120

125

Ser Ala Lys Met Glu Pro Gly Asn Val Asn Val Leu Gln Leu Ser Pro
130 135 140

Thr Val Gln Ala Thr Arg Ser Asn Tyr Thr Gln Ala His Arg Gly Ser
145 150 155 160

Val Pro Pro Tyr Val Asp Tyr Phe Leu Gly Arg Gly Arg Gly Arg Val
165 170 175

Leu Val Asp Val Leu Gln Ser Glu Gln Gly Ser Trp Phe Tyr Arg Lys
180 185 190

Arg Asn Arg Asn Met Val Val Glu Val Gln Glu Glu Val Pro Val Leu
195 200 205

Pro Asp Phe Cys Trp Leu Thr Leu Gly Gln Val Leu Ala Leu Leu Arg
210 215 220

Gln Asp Asn Ile Val Asn Met Asp Thr Arg Thr Val Leu Ser Cys Ile
225 230 235 240

Pro Phe His Asp Ser Ala Thr Gly Pro Glu Leu Ala Ala Ser Glu Glu
245 250 255

Pro Phe Arg Gln Ala Val Ala Arg Ser Leu Ser His Gly Ile Asp Ser
260 265 270

Ser Ser Ile Ser Glu Ala Val Gly Trp Phe Glu Glu Ala Lys Ala Arg
275 280 285

Tyr Arg Leu Arg Ala Thr Arg Val Pro Leu Ser Arg Val Asp Lys Trp
290 295 300

Tyr Arg Thr Asp Thr Glu Ile Ala His Gln Asp Gly Lys Tyr Phe Ala
305 310 315 320

Val Ile Ala Val Ser Val Ser Ala Thr Asn Arg Glu Val Ala Ser Trp
325 330 335

~~Thr Gln Pro Met Ile Glu Pro Arg Glu Gln Gly Glu Ile Ala Leu Leu~~
340 345 350

Val Lys Arg Ile Gly Gly Val Leu His Gly Leu Val His Ala Arg Val
355 360 365

Glu Ala Gly Tyr Lys Trp Thr Ala Glu Ile Ala Pro Thr Val Gln Cys

370

375

380

Ser Val Ala Asn Tyr Gln Ser Thr Pro Ser Asn Asp Trp Pro Pro Phe
 385 390 395 400

Leu Asp Asp Val Leu Thr Ala Asp Pro Glu Thr Val Arg Tyr Glu Ser
 405 410 415

Ile Leu Ser Glu Glu Gly Gly Arg Phe Tyr Gln Ala Gln Asn Arg Tyr
 420 425 430

Arg Ile Ile Glu Val His Glu Asp Phe Ala Ala Arg Pro Pro Ser Asp
 435 440 445

Phe Arg Trp Met Thr Leu Gly Gln Leu Gly Glu Leu Leu Arg Ser Thr
 450 455 460

His Phe Leu Asn Ile Gln Ala Arg Ser Leu Val Ala Ser Leu His Ser
 465 470 475 480

Leu Trp Ala Leu Gly Arg
 485

<210> 27

<211> 524

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(438)

<223> ORF11; Thioesterase

<400> 27

gtg agc aac gtg tgg ccg gaa aca tgg acg ccg ggg ttt ggc agg tgt 48
 Val Ser Asn Val Trp Pro Glu Thr Trp Thr Pro Gly Phe Gly Arg Cys
 1 5 10 15

tca tcg ctg ttg cgt cga ctc gga ttc cgc cgt gac cgg gac gat gcc 96
 Ser Ser Leu Leu Arg Arg Leu Gly Phe Arg Arg Asp Arg Asp Ala
 20 25 30

agg cga gtc ccg aag tca gat tct tgt cca gaa tcg tcc aat ggg gtg 144
 Arg Arg Val Pro Lys Ser Asp Ser Cys Pro Glu Ser Ser Asn Gly Val
 35 40 45

ttg atc tcc cca gag gtt tgc gct cca acc gat ttc cga cga gga tcg 192
 Leu Ile Ser Pro Glu Val Cys Ala Pro Thr Asp Phe Arg Arg Gly Ser
 50 55 60

tgg cgc ccg ctg agc aac gac tac cgt gcg gtc gag aca tac cgc tgt 240
 Trp Arg Pro Leu Ser Asn Asp Tyr Arg Ala Val Glu Thr Tyr Arg Cys
 65 70 75 80

gcg cca gga gcg aag gtg ggt tgc ccg atc acc gtg ctg gtg gta gat 288
 Ala Pro Gly Ala Lys Val Gly Cys Pro Ile Thr Val Leu Val Val Asp
 85 90 95

gcc gag ccg aag gtc acc ttg gat gag gcg gaa gcc tgg cga gag cac 336
 Ala Glu Pro Lys Val Thr Leu Asp Glu Ala Glu Ala Trp Arg Glu His
 100 105 110

acc gag gcc gtg gcc gac gtc cgt gtc ttc tcc ggc ggg cat ttc ttc 384
 Thr Glu Ala Val Ala Asp Val Arg Val Phe Ser Gly Gly His Phe Phe
 115 120 125

atg acc gaa cgc cag gac gag gtg ctc gcg gtc ctt acg ggc gga tcg 432
 Met Thr Glu Arg Gln Asp Glu Val Leu Ala Val Leu Thr Gly Gly Ser
 130 135 140

ctt cga tgatcctcgc caggccgctg gaccagaccg cgacgcccct gggagccggc 488
 Leu Arg
 145

gtgcacatcg tcacggcagt gagggattgg gcatga 524

<210> 28
 <211> 146
 <212> PRT
 <213> Saccharopolyspora spinosa

<400> 28
 Val Ser Asn Val Trp Pro Glu Thr Trp Thr Pro Gly Phe Gly Arg Cys
 1 5 10 15

Ser Ser Leu Leu Arg Arg Leu Gly Phe Arg Arg Asp Arg Asp Ala
 20 25 30

Arg Arg Val Pro Lys Ser Asp Ser Cys Pro Glu Ser Ser Asn Gly Val
 35 40 45

Leu Ile Ser Pro Glu Val Cys Ala Pro Thr Asp Phe Arg Arg Gly Ser
 50 55 60

Trp Arg Pro Leu Ser Asn Asp Tyr Arg Ala Val Glu Thr Tyr Arg Cys
65 70 75 80

Ala Pro Gly Ala Lys Val Gly Cys Pro Ile Thr Val Leu Val Val Asp
85 90 95

Ala Glu Pro Lys Val Thr Leu Asp Glu Ala Glu Ala Trp Arg Glu His
100 105 110

Thr Glu Ala Val Ala Asp Val Arg Val Phe Ser Gly Gly His Phe Phe
115 120 125

Met Thr Glu Arg Gln Asp Glu Val Leu Ala Val Leu Thr Gly Gly Ser
130 135 140

Leu Arg
145

<210> 29
<211> 1320
<212> DNA
<213> Saccharopolyspora spinosa

<220>
<221> CDS
<222> (1)..(1317)
<223> ORF12; Glycosyltransferase

<400> 29
atg cgt gtc ctg ttc acc ccg ctg ccg gcg agt tcg cac ttc ttc aac 48
Met Arg Val Leu Phe Thr Pro Leu Pro Ala Ser Ser His Phe Phe Asn
1 5 10 15

ctg gtg ccg ttg gcg tgg gcg ttg cgt gcc gcg ggg cac gag gtc cgt 96
Leu Val Pro Leu Ala Trp Ala Leu Arg Ala Ala Gly His Glu Val Arg
20 25 30

gtc gcc atc tgc ccg aat atg gtg tcg atg gtc acc gga gca gga ctc 144
~~Val Ala Ile Cys Pro Asn Met Val Ser Met Val Thr Gly Ala Gly Leu~~
35 40 45

acc gcg gtt ccc gtc ggc gac gag ctc gac ctc atc tcc ttg gcg gcc 192
Thr Ala Val Pro Val Gly Asp Glu Leu Asp Leu Ile Ser Leu Ala Ala
50 55 60

aag aac gaa gtt ctc ggc agc ggg gtc tcg gac gag aag ggg	240
Lys Asn Glu Leu Val Leu Gly Ser Gly Val Ser Phe Asp Glu Lys Gly	
65 70 75 80	
cgg cat ccg gaa ctc ttc gac gag ctg ctg tca atc aac tcc ggc aga	288
Arg His Pro Glu Leu Phe Asp Glu Leu Leu Ser Ile Asn Ser Gly Arg	
85 90 95	
gac acg gac gcc gtg gag caa ctc cac ctt gtg gat gac cga tcg ctg	336
Asp Thr Asp Ala Val Glu Gln Leu His Leu Val Asp Asp Arg Ser Leu	
100 105 110	
gac gat ctc atg ggg ttc gcc gag aaa tgg cag cct gat ctc gtt gtg	384
Asp Asp Leu Met Gly Phe Ala Glu Lys Trp Gln Pro Asp Leu Val Val	
115 120 125	
tgg gac gct atg gtg tgt tcg ggg cca gtt gtg gcg cga gcg ctc ggc	432
Trp Asp Ala Met Val Cys Ser Gly Pro Val Val Ala Arg Ala Leu Gly	
130 135 140	
gca cga cac gtg cgg atg ctc gtc gcc ctc gat gtg tcg ggg tgg ctg	480
Ala Arg His Val Arg Met Leu Val Ala Leu Asp Val Ser Gly Trp Leu	
145 150 155 160	
cgg tcc ggt ttc ctc gaa tac cag gaa tcg aag ccg cct gag cag cgc	528
Arg Ser Gly Phe Leu Glu Tyr Gln Glu Ser Lys Pro Pro Glu Gln Arg	
165 170 175	
gtc gac ccg ctc ggg acg tgg ctg gga gcg aag ctc gcc aag ttc gga	576
Val Asp Pro Leu Gly Thr Trp Leu Gly Ala Lys Leu Ala Lys Phe Gly	
180 185 190	
gcc acg ttc gat gaa gag atc gtg acg ggc caa gcg acc ata gat ccg	624
Ala Thr Phe Asp Glu Glu Ile Val Thr Gly Gln Ala Thr Ile Asp Pro	
195 200 205	
att cca tcc tgg atg cgc ctg cct gtg gac ttg gac tac atc tcg atg	672
Ile Pro Ser Trp Met Arg Leu Pro Val Asp Leu Asp Tyr Ile Ser Met	
210 215 220	
cgf ttc gtg ccg tac aac ggt ccg gcg gtg ttg ccg gag tgg ttg cgc	720
Arg Phe Val Pro Tyr Asn Gly Pro Ala Val Leu Pro Glu Trp Leu Arg	
225 230 235 240	
gaa cga ccg acg aag ccg cgc gtc tgc atc acg cgc ggg ctg acc aag	768
Glu Arg Pro Thr Lys Pro Arg Val Cys Ile Thr Arg Gly Leu Thr Lys	
245 250 255	

cgg cgg ctg agc agg gtg acc gaa cag tac ggg gag caa agt gac cag	816
Arg Arg Leu Ser Arg Val Thr Glu Gln Tyr Gly Glu Gln Ser Asp Gln	
260 265 270	
 gaa caa gca atg gtg gaa agg ttg ttg cgc ggc gcg gcc agg ctc gac	864
Glu Gln Ala Met Val Glu Arg Leu Leu Arg Gly Ala Ala Arg Leu Asp	
275 280 285	
 gtc gag gtg atc gcc acc ttg tct gac gac gaa gta cgg gag atg ggg	912
Val Glu Val Ile Ala Thr Leu Ser Asp Asp Glu Val Arg Glu Met Gly	
290 295 300	
 gag ttg ccc tcg aac gtc cgg gtc cac gaa tac gta ccg ctc aac gaa	960
Glu Leu Pro Ser Asn Val Arg Val His Glu Tyr Val Pro Leu Asn Glu	
305 310 315 320	
 ctg ctg gag tcg tgt tca gtg atc atc cat cat ggc tcg acg acg acg	1008
Leu Leu Glu Ser Cys Ser Val Ile Ile His His Gly Ser Thr Thr Thr	
325 330 335	
 cag gaa acc gcc acg gtc aac ggc gta ccg cag ttg att ctc cct ggg	1056
Gln Glu Thr Ala Thr Val Asn Gly Val Pro Gln Leu Ile Leu Pro Gly	
340 345 350	
 acc ttc tgg gac gaa tct cgt agg gcg gag ctc cta gcc gat cgg gga	1104
Thr Phe Trp Asp Glu Ser Arg Arg Ala Glu Leu Leu Ala Asp Arg Gly	
355 360 365	
 gcc ggt ctg gtc ctc gac ccc gcg acg ttt acc gaa gac gac gtg cga	1152
Ala Gly Leu Val Leu Asp Pro Ala Thr Phe Thr Glu Asp Asp Val Arg	
370 375 380	
 ggt cag ctg gcc cgc ctg ctc gac gag ccg tcg ttc gct gcc aac gcg	1200
Gly Gln Leu Ala Arg Leu Leu Asp Glu Pro Ser Phe Ala Ala Asn Ala	
385 390 395 400	
 gcg ctg atc cgc cgt gaa atc gag gaa agt ccc agc ccg cac gac atc	1248
Ala Leu Ile Arg Arg Glu Ile Glu Glu Ser Pro Ser Pro His Asp Ile	
405 410 415	
 gtt cca cgt ctg gaa aag cta gtt gcc gaa cgt gag aac cgc cgc act	1296
Val Pro Arg Leu Glu Lys Leu Val Ala Glu Arg Glu Asn Arg Arg Thr	
420 425 430	
 ggg cag tct gat ggc cat ccg tga	1320
Gly Gln Ser Asp Gly His Pro	
435	

<210> 30
<211> 439
<212> PRT
<213> Saccharopolyspora spinosa

<400> 30
Met Arg Val Leu Phe Thr Pro Leu Pro Ala Ser Ser His Phe Phe Asn
1 5 10 15
Leu Val Pro Leu Ala Trp Ala Leu Arg Ala Ala Gly His Glu Val Arg
20 25 30
Val Ala Ile Cys Pro Asn Met Val Ser Met Val Thr Gly Ala Gly Leu
35 40 45
Thr Ala Val Pro Val Gly Asp Glu Leu Asp Leu Ile Ser Leu Ala Ala
50 55 60
Lys Asn Glu Leu Val Leu Gly Ser Gly Val Ser Phe Asp Glu Lys Gly
65 70 75 80
Arg His Pro Glu Leu Phe Asp Glu Leu Leu Ser Ile Asn Ser Gly Arg
85 90 95
Asp Thr Asp Ala Val Glu Gln Leu His Leu Val Asp Asp Arg Ser Leu
100 105 110
Asp Asp Leu Met Gly Phe Ala Glu Lys Trp Gln Pro Asp Leu Val Val
115 120 125
Trp Asp Ala Met Val Cys Ser Gly Pro Val Val Ala Arg Ala Leu Gly
130 135 140
Ala Arg His Val Arg Met Leu Val Ala Leu Asp Val Ser Gly Trp Leu
145 150 155 160
Arg Ser Gly Phe Leu Glu Tyr Gln Glu Ser Lys Pro Pro Glu Gln Arg
165 170 175
Val Asp Pro Leu Gly Thr Trp Leu Gly Ala Lys Leu Ala Lys Phe Gly
180 185 190
Ala Thr Phe Asp Glu Glu Ile Val Thr Gly Gln Ala Thr Ile Asp Pro
195 200 205
Ile Pro Ser Trp Met Arg Leu Pro Val Asp Leu Asp Tyr Ile Ser Met
210 215 220

Arg Phe Val Pro Tyr Asn Gly Pro Ala Val Leu Pro Glu Trp Leu Arg
225 230 235 240

Glu Arg Pro Thr Lys Pro Arg Val Cys Ile Thr Arg Gly Leu Thr Lys
245 250 255

Arg Arg Leu Ser Arg Val Thr Glu Gln Tyr Gly Glu Gln Ser Asp Gln
260 265 270

Glu Gln Ala Met Val Glu Arg Leu Leu Arg Gly Ala Ala Arg Leu Asp
275 280 285

Val Glu Val Ile Ala Thr Leu Ser Asp Asp Glu Val Arg Glu Met Gly
290 295 300

Glu Leu Pro Ser Asn Val Arg Val His Glu Tyr Val Pro Leu Asn Glu
305 310 315 320

Leu Leu Glu Ser Cys Ser Val Ile Ile His His Gly Ser Thr Thr Thr
325 330 335

Gln Glu Thr Ala Thr Val Asn Gly Val Pro Gln Leu Ile Leu Pro Gly
340 345 350

Thr Phe Trp Asp Glu Ser Arg Arg Ala Glu Leu Leu Ala Asp Arg Gly
355 360 365

Ala Gly Leu Val Leu Asp Pro Ala Thr Phe Thr Glu Asp Asp Val Arg
370 375 380

Gly Gln Leu Ala Arg Leu Leu Asp Glu Pro Ser Phe Ala Ala Asn Ala
385 390 395 400

Ala Leu Ile Arg Arg Glu Ile Glu Glu Ser Pro Ser Pro His Asp Ile
405 410 415

Val Pro Arg Leu Glu Lys Leu Val Ala Glu Arg Glu Asn Arg Arg Thr
420 425 430

Gly Gln Ser Asp Gly His Pro
435

<210> 31
<211> 1389
<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1386)

<223> ORF13; 3,4-Dehydratase

<400> 31

atg cag agc cgg aaa acc aga gcg ctg ggg aaa ggg cgc gcc aga gtg 48
Met Gln Ser Arg Lys Thr Arg Ala Leu Gly Lys Gly Arg Ala Arg Val
1 5 10 15

act tcg tgt gac gac act tgc gct acc gct act gag atg gtg ccg gat 96
Thr Ser Cys Asp Asp Thr Cys Ala Thr Ala Thr Glu Met Val Pro Asp
20 25 30

gcc aag gac cgg ata ttg gca tcc gta cgc gat tac cac cgc gaa cag 144
Ala Lys Asp Arg Ile Leu Ala Ser Val Arg Asp Tyr His Arg Glu Gln
35 40 45

gaa tcc ccg acc ttc gtg gct gga tcg acg ccg atc cgg cca tcg ggc 192
Glu Ser Pro Thr Phe Val Ala Gly Ser Thr Pro Ile Arg Pro Ser Gly
50 55 60

gcc gtg ctc gac gag gac gac cgg gtg gca ctg gtg gaa gcc gcg ctg 240
Ala Val Leu Asp Glu Asp Asp Arg Val Ala Leu Val Glu Ala Ala Leu
65 70 75 80

gag ctc cgg atc gcc gcg ggc ggg aat gca cgg cga ttc gag agc gag 288
Glu Leu Arg Ile Ala Ala Gly Gly Asn Ala Arg Arg Phe Glu Ser Glu
85 90 95

ttc gcc cgc ttc ttc ggc ctc cgc aag gct cat ctc gtc aac tcc ggt 336
Phe Ala Arg Phe Phe Gly Leu Arg Lys Ala His Leu Val Asn Ser Gly
100 105 110

tcg tcg gcc aat ctc ctg gca ctg agt tcg ctt acc tcc ccc aaa ctc 384
Ser Ser Ala Asn Leu Leu Ala Leu Ser Ser Leu Thr Ser Pro Lys Leu
115 120 125

ggc gag gca cga ctg cgg ccc ggc gac gaa gtg atc act gcg gcg gtc 432
Gly Glu Ala Arg Leu Arg Pro Gly Asp Glu Val Ile Thr Ala Ala Val
130 135 140

ggc ttc ccc acg acg atc aat ccg gcg gtc caa aac gga ctc gtc ccg 480
Gly Phe Pro Thr Thr Ile Asn Pro Ala Val Gln Asn Gly Leu Val Pro
145 150 155 160

gta ttc gtc gac gtg gaa ctg ggc acc tac aac gca acg cca gac cgc 528
 Val Phe Val Asp Val Glu Leu Gly Thr Tyr Asn Ala Thr Pro Asp Arg
 165 170 175

atc aag gcc gcc gtc acg gaa cgg acg cga gcc atc atg ctg gcg cac 576
 Ile Lys Ala Ala Val Thr Glu Arg Thr Arg Ala Ile Met Leu Ala His
 180 185 190

acc ctg ggc aac ccc ttc gcc gct gac gaa atc gcg gag atc gca aaa 624
 Thr Leu Gly Asn Pro Phe Ala Ala Asp Glu Ile Ala Glu Ile Ala Lys
 195 200 205

gaa cac gag ctg ttc ctc gtc gaa gac aac tgt gat gcg gtg gga tcc 672
 Glu His Glu Leu Phe Leu Val Glu Asp Asn Cys Asp Ala Val Gly Ser
 210 215 220

acc tac cgg gga cgg ctg acc gga acc ttc ggc gac ctg aca acg gtc 720
 Thr Tyr Arg Gly Arg Leu Thr Gly Thr Phe Gly Asp Leu Thr Thr Val
 225 230 235 240

agc ttc tat cct gcc cat cac atc acc agc ggc gag ggt ggc tgc gtg 768
 Ser Phe Tyr Pro Ala His His Ile Thr Ser Gly Glu Gly Gly Cys Val
 245 250 255

ttg acc ggc agc ctg gaa ttg gct cgc atc atc gag tcg ctg cgt gac 816
 Leu Thr Gly Ser Leu Glu Leu Ala Arg Ile Ile Glu Ser Leu Arg Asp
 260 265 270

tgg gga cgg gat tgc tgg tgc gag ccc ggc gtg gac aac acc tgc cgc 864
 Trp Gly Arg Asp Cys Trp Cys Glu Pro Gly Val Asp Asn Thr Cys Arg
 275 280 285

aag agg ttc gac tac cac ctc ggt acc ctt cca ccg ggc tac gac cac 912
 Lys Arg Phe Asp Tyr His Leu Gly Thr Leu Pro Pro Gly Tyr Asp His
 290 295 300

aag tac acg ttc tcc cac gtc ggt tac aac ctc aag acc acc gac ctg 960
 Lys Tyr Thr Phe Ser His Val Gly Tyr Asn Leu Lys Thr Thr Asp Leu
 305 310 315 320

cag gcc gca ctt gcg ctg agc cag ttg agc aag att tcc gca ttc ggg 1008
 Gln Ala Ala Leu Ala Leu Ser Gln Leu Ser Lys Ile Ser Ala Phe Gly
 325 330 335

tcg gca cgc cgc cgt aac tgg cga cgg ttg cgc gaa ggg ctg tcc ggg 1056
 Ser Ala Arg Arg Arg Asn Trp Arg Arg Leu Arg Glu Gly Leu Ser Gly
 340 345 350

ttg ccg ggc ctg ctg ctg ccg gta gcc aca ccg cac agc gac ccg agc 1104
 Leu Pro Gly Leu Leu Leu Pro Val Ala Thr Pro His Ser Asp Pro Ser
 355 360 365

tgg ttc ggg ttt gcg atc acc atc agt gcg gac gcc ggg ttc acc cgt 1152
 Trp Phe Gly Phe Ala Ile Thr Ile Ser Ala Asp Ala Gly Phe Thr Arg
 370 375 380

gcc gcc ctg gtg aac ttc ctg gaa tcc cgc aac atc ggc acc cga ctg 1200
 Ala Ala Leu Val Asn Phe Leu Glu Ser Arg Asn Ile Gly Thr Arg Leu
 385 390 395 400

ctg ttc ggc ggt aac atc acc cgg cac ccg gcc ttc gag cag gtg cgg 1248
 Leu Phe Gly Gly Asn Ile Thr Arg His Pro Ala Phe Glu Gln Val Arg
 405 410 415

tac ccg atc gcc gac gcg ctc acc aac agc gac atc gtc acc gac cga 1296
 Tyr Arg Ile Ala Asp Ala Leu Thr Asn Ser Asp Ile Val Thr Asp Arg
 420 425 430

acc ttc tgg gtc ggc gtc tac cca ggc ata acg gac caa atg atc gac 1344
 Thr Phe Trp Val Gly Val Tyr Pro Gly Ile Thr Asp Gln Met Ile Asp
 435 440 445

tac gtc gtc gaa tca atc gct gaa ttc gtg gcc aag agt tcc tag 1389
 Tyr Val Val Glu Ser Ile Ala Glu Phe Val Ala Lys Ser Ser
 450 455 460

<210> 32

<211> 462

<212> PRT

<213> Saccharopolyspora spinosa

<400> 32

Met Gln Ser Arg Lys Thr Arg Ala Leu Gly Lys Gly Arg Ala Arg Val
 1 5 10 15

Thr Ser Cys Asp Asp Thr Cys Ala Thr Ala Thr Glu Met Val Pro Asp
 20 25 30

Ala Lys Asp Arg Ile Leu Ala Ser Val Arg Asp Tyr His Arg Glu Gln
 35 40 45

Glu Ser Pro Thr Phe Val Ala Gly Ser Thr Pro Ile Arg Pro Ser Gly
 50 55 60

Ala Val Leu Asp Glu Asp Asp Arg Val Ala Leu Val Glu Ala Ala Leu

325

330

335

Ser Ala Arg Arg Arg Asn Trp Arg Arg Leu Arg Glu Gly Leu Ser Gly
 340 345 350

Leu Pro Gly Leu Leu Leu Pro Val Ala Thr Pro His Ser Asp Pro Ser
 355 360 365

Trp Phe Gly Phe Ala Ile Thr Ile Ser Ala Asp Ala Gly Phe Thr Arg
 370 375 380

Ala Ala Leu Val Asn Phe Leu Glu Ser Arg Asn Ile Gly Thr Arg Leu
 385 390 395 400

Leu Phe Gly Gly Asn Ile Thr Arg His Pro Ala Phe Glu Gln Val Arg
 405 410 415

Tyr Arg Ile Ala Asp Ala Leu Thr Asn Ser Asp Ile Val Thr Asp Arg
 420 425 430

Thr Phe Trp Val Gly Val Tyr Pro Gly Ile Thr Asp Gln Met Ile Asp
 435 440 445

Tyr Val Val Glu Ser Ile Ala Glu Phe Val Ala Lys Ser Ser
 450 455 460

<210> 33

<211> 1158

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1155)

<223> ORF14; 4-Aminotransferase

<400> 33

gtg atc aac ctg cac cag ccg atc ctc ggc acc gaa gaa ctc gac gcg 48

Val Ile Asn Leu His Gln Pro Ile Leu Gly Thr Glu Glu Leu Asp Ala

1

5

10

15

atc gcg gag gtg ttc gcc tcc aac tgg atc ggg ctc ggg ccg cgc acc 96

Ile Ala Glu Val Phe Ala Ser Asn Trp Ile Gly Leu Gly Pro Arg Thr

20

25

30

cgg acg ttc gag gcc gaa ttc gcc cac cac ctg gga gtg gat ccc gaa 144

Arg Thr Phe Glu Ala Glu Phe Ala His His Leu Gly Val Asp Pro Glu	
35 40 45	
cag gtc gtg ttc ctc aac tcg ggg act gcc gcg ctg ttc ctt acc gtg	192
Gln Val Val Phe Leu Asn Ser Gly Thr Ala Ala Leu Phe Leu Thr Val	
50 55 60	
cag gtg ctc gac ctc ggc cca ggc gac gac gtg gta ctt cct tcg ata	240
Gln Val Leu Asp Leu Gly Pro Gly Asp Asp Val Val Leu Pro Ser Ile	
65 70 75 80	
agc ttc gtg gcg gcg gcc aac gcc atc gca tcc tcc ggt gcc cgc ccg	288
Ser Phe Val Ala Ala Ala Asn Ala Ile Ala Ser Ser Gly Ala Arg Pro	
85 90 95	
gtg ttc tgc gac gtc gac ccc cgg acg ttg aac ccc acg ctg gat gat	336
Val Phe Cys Asp Val Asp Pro Arg Thr Leu Asn Pro Thr Leu Asp Asp	
100 105 110	
gtg gcg agg gcc atc acg ccg gcg acc aag gcc gta ttg ctg ctc cac	384
Val Ala Arg Ala Ile Thr Pro Ala Thr Lys Ala Val Leu Leu Leu His	
115 120 125	
tat gga gga tcg ccg gga gaa gtc acc gcg atc gcc gat ttc tgc cgt	432
Tyr Gly Gly Ser Pro Gly Glu Val Thr Ala Ile Ala Asp Phe Cys Arg	
130 135 140	
gaa aag ggc ctc atg ctc atc gag gac tcc gcc tgc gcg gtg gca tcg	480
Glu Lys Gly Leu Met Leu Ile Glu Asp Ser Ala Cys Ala Val Ala Ser	
145 150 155 160	
tcc gtg cac ggc acc gct tgc gga acc ttt ggt gac ctg gcc acg tgg	528
Ser Val His Gly Thr Ala Cys Gly Thr Phe Gly Asp Leu Ala Thr Trp	
165 170 175	
agt ttc gat gcg atg aag atc ctg gtc acc ggg gat ggg ggc atg ttc	576
Ser Phe Asp Ala Met Lys Ile Leu Val Thr Gly Asp Gly Gly Met Phe	
180 185 190	
tac gcg gcg gat ccg gag ctg gcg cac cgc gca aga cga ctc gcc tac	624
Tyr Ala Ala Asp Pro Glu Leu Ala His Arg Ala Arg Arg Leu Ala Tyr	
195 200 205	
cac ggt ctt gag cag atg agc gga ttc gat tcg gcc aag tct tcc aac	672
His Gly Leu Glu Gln Met Ser Gly Phe Asp Ser Ala Lys Ser Ser Asn	
210 215 220	
cgc tgg tgg gat att cgc gtc gaa gac atc ggc cag cgg ctg atc ggg	720

Arg Trp Trp Asp Ile Arg Val Glu Asp Ile Gly Gln Arg Leu Ile Gly
 225 230 235 240

aac gac atg acg gca gcg ctt ggc agc gtg cag ctg cgc aaa ctg cca 768
 Asn Asp Met Thr Ala Ala Leu Gly Ser Val Gln Leu Arg Lys Leu Pro
 245 250 255

gaa ttc atc aac agg cgt aga gaa atc gct acg cag tac gac cgg ttg 816
 Glu Phe Ile Asn Arg Arg Arg Glu Ile Ala Thr Gln Tyr Asp Arg Leu
 260 265 270

ctt tcc gat gtg ccg ggt gtc ctc cta ccg ccg acg cta ccg gat ggg 864
 Leu Ser Asp Val Pro Gly Val Leu Leu Pro Pro Thr Leu Pro Asp Gly
 275 280 285

cac gtc tcg tca cac tac ttc tac tgg gtc cag ctg gct ccg gag atc 912
 His Val Ser Ser His Tyr Phe Tyr Trp Val Gln Leu Ala Pro Glu Ile
 290 295 300

cgc gac cag gtg gcg cag caa atg ctg gaa cgc ggc atc tac acg agc 960
 Arg Asp Gln Val Ala Gln Gln Met Leu Glu Arg Gly Ile Tyr Thr Ser
 305 310 315 320

tac cgc tac ccg ccc ctg cac aag gtc ccc atc tac cgc gcg gac tgc 1008
 Tyr Arg Tyr Pro Pro Leu His Lys Val Pro Ile Tyr Arg Ala Asp Cys
 325 330 335

aag ctg cct tct gcg gag cac gcc tgc cgc aga aca ctc ctg cta cca 1056
 Lys Leu Pro Ser Ala Glu His Ala Cys Arg Arg Thr Leu Leu Leu Pro
 340 345 350

ctg cac cca agc ctt gac gac gcc gag gtg cgc acg gtg gct gac gag 1104
 Leu His Pro Ser Leu Asp Asp Ala Glu Val Arg Thr Val Ala Asp Glu
 355 360 365

ttc cag aag gcc gtc gaa cac cac atc agc caa aga tca cca ctc cga 1152
 Phe Gln Lys Ala Val Glu His His Ile Ser Gln Arg Ser Pro Leu Arg
 370 375 380

aag tga 1158
 Lys
 385

<210> 34

<211> 385

<212> PRT

<213> Saccharopolyspora spinosa

<400> 34

Val Ile Asn Leu His Gln Pro Ile Leu Gly Thr Glu Glu Leu Asp Ala
1 5 10 15

Ile Ala Glu Val Phe Ala Ser Asn Trp Ile Gly Leu Gly Pro Arg Thr
20 25 30

Arg Thr Phe Glu Ala Glu Phe Ala His His Leu Gly Val Asp Pro Glu
35 40 45

Gln Val Val Phe Leu Asn Ser Gly Thr Ala Ala Leu Phe Leu Thr Val
50 55 60

Gln Val Leu Asp Leu Gly Pro Gly Asp Asp Val Val Leu Pro Ser Ile
65 70 75 80

Ser Phe Val Ala Ala Ala Asn Ala Ile Ala Ser Ser Gly Ala Arg Pro
85 90 95

Val Phe Cys Asp Val Asp Pro Arg Thr Leu Asn Pro Thr Leu Asp Asp
100 105 110

Val Ala Arg Ala Ile Thr Pro Ala Thr Lys Ala Val Leu Leu Leu His
115 120 125

Tyr Gly Gly Ser Pro Gly Glu Val Thr Ala Ile Ala Asp Phe Cys Arg
130 135 140

Glu Lys Gly Leu Met Leu Ile Glu Asp Ser Ala Cys Ala Val Ala Ser
145 150 155 160

Ser Val His Gly Thr Ala Cys Gly Thr Phe Gly Asp Leu Ala Thr Trp
165 170 175

Ser Phe Asp Ala Met Lys Ile Leu Val Thr Gly Asp Gly Gly Met Phe
180 185 190

Tyr Ala Ala Asp Pro Glu Leu Ala His Arg Ala Arg Arg Leu Ala Tyr
195 200 205

His Gly Leu Glu Gln Met Ser Gly Phe Asp Ser Ala Lys Ser Ser Asn
210 215 220

Arg Trp Trp Asp Ile Arg Val Glu Asp Ile Gly Gln Arg Leu Ile Gly
225 230 235 240

Asn Asp Met Thr Ala Ala Leu Gly Ser Val Gln Leu Arg Lys Leu Pro

245

250

255

Glu Phe Ile Asn Arg Arg Arg Glu Ile Ala Thr Gln Tyr Asp Arg Leu
 260 265 270

Leu Ser Asp Val Pro Gly Val Leu Leu Pro Pro Thr Leu Pro Asp Gly
 275 280 285

His Val Ser Ser His Tyr Phe Tyr Trp Val Gln Leu Ala Pro Glu Ile
 290 295 300

Arg Asp Gln Val Ala Gln Gln Met Leu Glu Arg Gly Ile Tyr Thr Ser
 305 310 315 320

Tyr Arg Tyr Pro Pro Leu His Lys Val Pro Ile Tyr Arg Ala Asp Cys
 325 330 335

Lys Leu Pro Ser Ala Glu His Ala Cys Arg Arg Thr Leu Leu Leu Pro
 340 345 350

Leu His Pro Ser Leu Asp Asp Ala Glu Val Arg Thr Val Ala Asp Glu
 355 360 365

Phe Gln Lys Ala Val Glu His His Ile Ser Gln Arg Ser Pro Leu Arg
 370 375 380

Lys
 385

<210> 35

<211> 750

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(747)

<223> ORF15; N-Dimethyltransferase

<400> 35

atg tcg cgc gtg agc gac aca ttc gca gaa acc tcc tcg gta tac agc 48
 Met Ser Arg Val Ser Asp Thr Phe Ala Glu Thr Ser Ser Val Tyr Ser
 1 5 10 15

cca gat cat gcc gac atc tac gac gcg atc cac tcc gcg cgt ggc cgg 96
 Pro Asp His Ala Asp Ile Tyr Asp Ala Ile His Ser Ala Arg Gly Arg

20

25

30

gac tgg gca gcc gag gcc ggg gaa gta gtc cag ctc gta cgc acc agg 144
 Asp Trp Ala Ala Glu Ala Gly Glu Val Val Gln Leu Val Arg Thr Arg
 35 40 45

ctg ccc gaa gca cag tcc cta ctc gac gtc gcc tgt ggg acc ggg gcg 192
 Leu Pro Glu Ala Gln Ser Leu Leu Asp Val Ala Cys Gly Thr Gly Ala
 50 55 60

cac cta gag cga ttc cgt gcc gaa tac gcg aag gtc gcg ggg ctt gaa 240
 His Leu Glu Arg Phe Arg Ala Glu Tyr Ala Lys Val Ala Gly Leu Glu
 65 70 75 80

ctg tcc gat gcg atg cgg gag atc gcg atc aga cga gtc cct gag gta 288
 Leu Ser Asp Ala Met Arg Glu Ile Ala Ile Arg Arg Val Pro Glu Val
 85 90 95

ccg att cac atc ggt gac atc cgc gat ttc gac ctc ggc gag cca ttc 336
 Pro Ile His Ile Gly Asp Ile Arg Asp Phe Asp Leu Gly Glu Pro Phe
 100 105 110

gac gtc atc acc tgc ctg tgc ttt acc gcg gct tac atg cgg acc gtt 384
 Asp Val Ile Thr Cys Leu Cys Phe Thr Ala Ala Tyr Met Arg Thr Val
 115 120 125

gac gac ctg cga cgc gtg acg cgg aac atg gcc cgg cac ctg gcc cct 432
 Asp Asp Leu Arg Arg Val Thr Arg Asn Met Ala Arg His Leu Ala Pro
 130 135 140

ggt gga gtc gcg gtc atc gaa ccc tgg tgg ttt ccc gac aag ttc atc 480
 Gly Gly Val Ala Val Ile Glu Pro Trp Trp Phe Pro Asp Lys Phe Ile
 145 150 155 160

gac ggg ttc gtc acc gga gcc gtc gcg cac cac ggc gag cgg gtg atc 528
 Asp Gly Phe Val Thr Gly Ala Val Ala His His Gly Glu Arg Val Ile
 165 170 175

agc cgg cta tcg cac tcg gtc ctg gag ggc cgt acg agc cgg atg acc 576
 Ser Arg Leu Ser His Ser Val Leu Glu Gly Arg Thr Ser Arg Met Thr
 180 185 190

gtc cgc tac aca gtc gcc gaa ccc acc ggg atc cgg gac ttc aca gag 624
 Val Arg Tyr Thr Val Ala Glu Pro Thr Gly Ile Arg Asp Phe Thr Glu
 195 200 205

ttc gaa atc ctc tcg ctg ttc act gag gac gag tac acc gcc gcg ctc 672
 Phe Glu Ile Leu Ser Leu Phe Thr Glu Asp Glu Tyr Thr Ala Ala Leu

210

215

220

gaa gac gca ggg atc cgc gcg gaa tac ctt cct gga gca ccg aac ggc 720
 Glu Asp Ala Gly Ile Arg Ala Glu Tyr Leu Pro Gly Ala Pro Asn Gly
 225 230 235 240

cga ggc ctg ttc gtc gga atc cgc aac tga 750
 Arg Gly Leu Phe Val Gly Ile Arg Asn
 245

<210> 36

<211> 249

<212> PRT

<213> Saccharopolyspora spinosa

<400> 36

Met Ser Arg Val Ser Asp Thr Phe Ala Glu Thr Ser Ser Val Tyr Ser
 1 5 10 15

Pro Asp His Ala Asp Ile Tyr Asp Ala Ile His Ser Ala Arg Gly Arg
 20 25 30

Asp Trp Ala Ala Glu Ala Gly Glu Val Val Gln Leu Val Arg Thr Arg
 35 40 45

Leu Pro Glu Ala Gln Ser Leu Leu Asp Val Ala Cys Gly Thr Gly Ala
 50 55 60

His Leu Glu Arg Phe Arg Ala Glu Tyr Ala Lys Val Ala Gly Leu Glu
 65 70 75 80

Leu Ser Asp Ala Met Arg Glu Ile Ala Ile Arg Arg Val Pro Glu Val
 85 90 95

Pro Ile His Ile Gly Asp Ile Arg Asp Phe Asp Leu Gly Glu Pro Phe
 100 105 110

Asp Val Ile Thr Cys Leu Cys Phe Thr Ala Ala Tyr Met Arg Thr Val
 115 120 125

Asp Asp Leu Arg Arg Val Thr Arg Asn Met Ala Arg His Leu Ala Pro
 130 135 140

Gly Gly Val Ala Val Ile Glu Pro Trp Trp Phe Pro Asp Lys Phe Ile
 145 150 155 160

Asp Gly Phe Val Thr Gly Ala Val Ala His His Gly Glu Arg Val Ile

165	170	175
Ser Arg Leu Ser His Ser Val Leu Glu Gly Arg Thr Ser Arg Met Thr		
180	185	190
Val Arg Tyr Thr Val Ala Glu Pro Thr Gly Ile Arg Asp Phe Thr Glu		
195	200	205
Phe Glu Ile Leu Ser Leu Phe Thr Glu Asp Glu Tyr Thr Ala Ala Leu		
210	215	220
Glu Asp Ala Gly Ile Arg Ala Glu Tyr Leu Pro Gly Ala Pro Asn Gly		
225	230	235
240		
Arg Gly Leu Phe Val Gly Ile Arg Asn		
245		

<210> 37
 <211> 726
 <212> DNA
 <213> Saccharopolyspora spinosa

<220>
 <221> CDS
 <222> (1)..(723)
 <223> ORF16; 3,4-Reduktase

<400> 37
 atg agc gaa cag acg att gca ctg gtc acc ggc gca aac aag gga atc 48
 Met Ser Glu Gln Thr Ile Ala Leu Val Thr Gly Ala Asn Lys Gly Ile
 1 5 10 15
 gga tac gag atc gcg gcc ggg ctc ggc gcg ctg ggg tgg agc gtc gga 96
 Gly Tyr Glu Ile Ala Ala Gly Leu Gly Ala Leu Gly Trp Ser Val Gly
 20 25 30
 atc ggg gca cgg gac cac cag cgc ggg gag gat gcc gtg gcg aaa ttg 144
 Ile Gly Ala Arg Asp His Gln Arg Gly Glu Asp Ala Val Ala Lys Leu
 35 40 45

cgt gcg gac ggc gtc gat gcg ttc gcg gta tcc ctg gac gtg aca gac 192
 Arg Ala Asp Gly Val Asp Ala Phe Ala Val Ser Leu Asp Val Thr Asp
 50 55 60

gac gcg agc gtc gcg gct gct gcg gct ctg ctc gag gag cgc gcc ggc 240
 Asp Ala Ser Val Ala Ala Ala Ala Ala Leu Leu Glu Glu Arg Ala Gly

65

70

75

80

cgg ctc gat gtg ctg gtt aat aac gcc ggc atc gcc ggg gca tgg ccg 288
 Arg Leu Asp Val Leu Val Asn Asn Ala Gly Ile Ala Gly Ala Trp Pro
 85 90 95

gag gag ccc tcg acc gtc aca ccg gcg agc ctc cgg gcg gtg gtg gag 336
 Glu Glu Pro Ser Thr Val Thr Pro Ala Ser Leu Arg Ala Val Val Glu
 100 105 110

acc aac gtg atc ggc gtc gtt cgg gtt acc aac gct atg ctg ccg ttg 384
 Thr Asn Val Ile Gly Val Val Arg Val Thr Asn Ala Met Leu Pro Leu
 115 120 125

cta cgc cgc tcc gag cgc ccg cgg atc gtc aac cag tcc agc cac gtc 432
 Leu Arg Arg Ser Glu Arg Pro Arg Ile Val Asn Gln Ser Ser His Val
 130 135 140

gct tcc ctg acc ttg caa acc acg ccg ggc gtc gac ctc ggc ggg atc 480
 Ala Ser Leu Thr Leu Gln Thr Thr Pro Gly Val Asp Leu Gly Gly Ile
 145 150 155 160

agc gga gcc tac tca ccg tcg aag acg ttc ctc aac gcg atc acc atc 528
 Ser Gly Ala Tyr Ser Pro Ser Lys Thr Phe Leu Asn Ala Ile Thr Ile
 165 170 175

cag tac gcc aag gaa ctc agc gat acc aac atc aaa atc aac aac gcc 576
 Gln Tyr Ala Lys Glu Leu Ser Asp Thr Asn Ile Lys Ile Asn Asn Ala
 180 185 190

tgc ccc ggc tac gtc gcg acc gac ctt aac ggc ttc cac gga acc agc 624
 Cys Pro Gly Tyr Val Ala Thr Asp Leu Asn Gly Phe His Gly Thr Ser
 195 200 205

acg ccg gca gac ggt gcc agg atc gcc att cgg ctc gcc acg ctg cca 672
 Thr Pro Ala Asp Gly Ala Arg Ile Ala Ile Arg Leu Ala Thr Leu Pro
 210 215 220

gac gac ggc ccg acc gga ggc atg ttc gac gac gcc ggg aat gtg ccc 720
 Asp Asp Gly Pro Thr Gly Gly Met Phe Asp Asp Ala Gly Asn Val Pro
 225 230 235 240

tgg tga 726
 Trp

<210> 38

<211> 241

<212> PRT

<213> *Saccharopolyspora spinosa*

<400> 38

Met Ser Glu Gln Thr Ile Ala Leu Val Thr Gly Ala Asn Lys Gly Ile
1 5 10 15

Gly Tyr Glu Ile Ala Ala Gly Leu Gly Ala Leu Gly Trp Ser Val Gly
20 25 30

Ile Gly Ala Arg Asp His Gln Arg Gly Glu Asp Ala Val Ala Lys Leu
35 40 45

Arg Ala Asp Gly Val Asp Ala Phe Ala Val Ser Leu Asp Val Thr Asp
50 55 60

Asp Ala Ser Val Ala Ala Ala Ala Ala Leu Leu Glu Glu Arg Ala Gly
65 70 75 80

Arg Leu Asp Val Leu Val Asn Asn Ala Gly Ile Ala Gly Ala Trp Pro
85 90 95

Glu Glu Pro Ser Thr Val Thr Pro Ala Ser Leu Arg Ala Val Val Glu
100 105 110

Thr Asn Val Ile Gly Val Val Arg Val Thr Asn Ala Met Leu Pro Leu
115 120 125

Leu Arg Arg Ser Glu Arg Pro Arg Ile Val Asn Gln Ser Ser His Val
130 135 140

Ala Ser Leu Thr Leu Gln Thr Thr Pro Gly Val Asp Leu Gly Gly Ile
145 150 155 160

Ser Gly Ala Tyr Ser Pro Ser Lys Thr Phe Leu Asn Ala Ile Thr Ile
165 170 175

Gln Tyr Ala Lys Glu Leu Ser Asp Thr Asn Ile Lys Ile Asn Asn Ala
180 185 190

Cys Pro Gly Tyr Val Ala Thr Asp Leu Asn Gly Phe His Gly Thr Ser
195 200 205

Thr Pro Ala Asp Gly Ala Arg Ile Ala Ile Arg Leu Ala Thr Leu Pro
210 215 220

Asp Asp Gly Pro Thr Gly Gly Met Phe Asp Asp Ala Gly Asn Val Pro
225 230 235 240

Trp

<210> 39

<211> 837

<212> DNA

<213> *Saccharopolyspora spinosa*

<220>

<221> CDS

<222> (1)..(834)

<223> ORF17; Transkriptions-Regulator

<400> 39

atg gag acg cgg gag ttg cgg tac ttc gtt gca gtc gcc gag gag ttg 48

Met Glu Thr Arg Glu Leu Arg Tyr Phe Val Ala Val Ala Glu Glu Leu

1

5

10

15

cac ttc ggc cgg gcc gcc cag cgc ctg ggc atc gcc cag ccg ccg ctg 96

His Phe Gly Arg Ala Ala Gln Arg Leu Gly Ile Ala Gln Pro Pro Leu

20

25

30

tcg cgg acg atc gcc cag ctc gag caa cga ctc gga gtc gtg ttg ctg 144

Ser Arg Thr Ile Ala Gln Leu Glu Gln Arg Leu Gly Val Val Leu Leu

35

40

45

caa cgc acc agc cgc aaa gtc tcg ctc acc gaa gcc ggg gca atg ctg 192

Gln Arg Thr Ser Arg Lys Val Ser Leu Thr Glu Ala Gly Ala Met Leu

50

55

60

ctg acc gaa ggc cgg gcg atc ctc ggc gcg ctg gca gca gcc gag cga 240

Leu Thr Glu Gly Arg Ala Ile Leu Gly Ala Leu Ala Ala Ala Glu Arg

65

70

75

80

cgc acc cag cgt gcc gcg acg agc cag ccc tcg cta gtc ctg gct gcc 288

Arg Thr Gln Arg Ala Ala Thr Ser Gln Pro Ser Leu Val Leu Ala Ala

85

90

95

aag gcc ggc gcc tcc ggt gag ctg ctg gcg aag ttg ctc gac gcg tac 336

Lys Ala Gly Ala Ser Gly Glu Leu Leu Ala Lys Leu Leu Asp Ala Tyr

100

105

110

gcc gcc gag ccg gga gcc gtg gcc gtc gac ctg ctg ctc tgc gaa tcc 384

Ala Ala Glu Pro Gly Ala Val Ala Val Asp Leu Leu Cys Glu Ser

115

120

125

cag ccc cag aaa acg ctg cat gac ggc cgg gcc gac gtg gcg ctg ttg	432
Gln Pro Gln Lys Thr Leu His Asp Gly Arg Ala Asp Val Ala Leu Leu	
130 135 140	
cat caa ccc ttc gac ccg acg gcc gaa ctc gac atc gaa att ctg aac	480
His Gln Pro Phe Asp Pro Thr Ala Glu Leu Asp Ile Glu Ile Leu Asn	
145 150 155 160	
acc gag caa caa gtc gcc att ctt ccg acc tcg cat ccg ctt gcc agc	528
Thr Glu Gln Gln Val Ala Ile Leu Pro Thr Ser His Pro Leu Ala Ser	
165 170 175	
gag ccc cat gta cgg atg gcg gat gtc agc tca ctg ccg gat ctc ccg	576
Glu Pro His Val Arg Met Ala Asp Val Ser Ser Leu Pro Asp Leu Pro	
180 185 190	
ctt gcg cgc tgg ccc ggc ccc gac ggc gtc tat cca gat ggc ccc ggc	624
Leu Ala Arg Trp Pro Gly Pro Asp Gly Val Tyr Pro Asp Gly Pro Gly	
195 200 205	
gtg gaa gta cgc aac cag acg caa ctg ttc caa atg atc gca ctc ggc	672
Val Glu Val Arg Asn Gln Thr Gln Leu Phe Gln Met Ile Ala Leu Gly	
210 215 220	
cgc act acc gtg gtc atg ccc gaa tcc agt cgc gtc aac ctg ctc gaa	720
Arg Thr Thr Val Val Met Pro Glu Ser Ser Arg Val Asn Leu Leu Glu	
225 230 235 240	
ggc ctc gcc gcc gta ccg gtt cta gac gcg ccg gac gtg acg aca gtc	768
Gly Leu Ala Ala Val Pro Val Leu Asp Ala Pro Asp Val Thr Thr Val	
245 250 255	
atc gcc tgg ccg ccc cac agc cgc tcc cga gca ctc gcc ggc ttg gtc	816
Ile Ala Trp Pro Pro His Ser Arg Ser Arg Ala Leu Ala Gly Leu Val	
260 265 270	
cgc gtg gcc aca ctc ctc taa	837
Arg Val Ala Thr Leu Leu	
275	

<210> 40
 <211> 278
 <212> PRT
 <213> Saccharopolyspora spinosa

<400> 40

Met Glu Thr Arg Gln Leu Arg Tyr Phe Val Ala Val Ala Leu Glu Leu
1 5 10 15

His Phe Gly Arg Ala Ala Gln Arg Leu Gly Ile Ala Gln Pro Pro Leu
20 25 30

Ser Arg Thr Ile Ala Gln Leu Glu Gln Arg Leu Gly Val Val Leu Leu
35 40 45

Gln Arg Thr Ser Arg Lys Val Ser Leu Thr Glu Ala Gly Ala Met Leu
50 55 60

Leu Thr Glu Gly Arg Ala Ile Leu Gly Ala Leu Ala Ala Ala Glu Arg
65 70 75 80

Arg Thr Gln Arg Ala Ala Thr Ser Gln Pro Ser Leu Val Leu Ala Ala
85 90 95

Lys Ala Gly Ala Ser Gly Glu Leu Leu Ala Lys Leu Leu Asp Ala Tyr
100 105 110

Ala Ala Glu Pro Gly Ala Val Ala Val Asp Leu Leu Leu Cys Glu Ser
115 120 125

Gln Pro Gln Lys Thr Leu His Asp Gly Arg Ala Asp Val Ala Leu Leu
130 135 140

His Gln Pro Phe Asp Pro Thr Ala Glu Leu Asp Ile Glu Ile Leu Asn
145 150 155 160

Thr Glu Gln Gln Val Ala Ile Leu Pro Thr Ser His Pro Leu Ala Ser
165 170 175

Glu Pro His Val Arg Met Ala Asp Val Ser Ser Leu Pro Asp Leu Pro
180 185 190

Leu Ala Arg Trp Pro Gly Pro Asp Gly Val Tyr Pro Asp Gly Pro Gly
195 200 205

Val Glu Val Arg Asn Gln Thr Gln Leu Phe Gln Met Ile Ala Leu Gly
210 215 220

Arg Thr Thr Val Val Met Pro Glu Ser Ser Arg Val Asn Leu Leu Glu
225 230 235 240

Gly Leu Ala Ala Val Pro Val Leu Asp Ala Pro Asp Val Thr Thr Val
245 250 255

Ile Ala Trp Pro Pro His Ser Arg Ser Arg Ala Leu Ala Gly Leu Val
 260 265 270

Arg Val Ala Thr Leu Leu
 275

<210> 41
 <211> 7788
 <212> DNA
 <213> Saccharopolyspora spinosa

<220>
 <221> CDS
 <222> (1)..(7785)
 <223> ORF18; Polyketidsynthase

<400> 41
 atg agc gaa gcc ggg aac ctg ata gcc gtc atc gga ctg tcc tgc cgc 48
 Met Ser Glu Ala Gly Asn Leu Ile Ala Val Ile Gly Leu Ser Cys Arg
 1 5 10 15

cta ccc cag gcg cct gac ccg gct tcc ttc tgg cgg ttg ctg cgc acc 96
 Leu Pro Gln Ala Pro Asp Pro Ala Ser Phe Trp Arg Leu Leu Arg Thr
 20 25 30

gga acg gac gcc atc acc acg gtc ccg gaa ggg cgg tgg ggc gac ccg 144
 Gly Thr Asp Ala Ile Thr Thr Val Pro Glu Gly Arg Trp Gly Asp Pro
 35 40 45

ttg cct ggt cgg gat gcg ccc aag ggc ccg gaa tgg ggt ggt ttc ctg 192
 Leu Pro Gly Arg Asp Ala Pro Lys Gly Pro Glu Trp Gly Gly Phe Leu
 50 55 60

gct gat gtc gac tgc ttc gat ccc gag ttc ttc ggg atc tcg ccg cga 240
 Ala Asp Val Asp Cys Phe Asp Pro Glu Phe Phe Gly Ile Ser Pro Arg
 65 70 75 80

gaa gcg gca gcc gtg gat ccc cag cag agg ctg gct ctg gag ctc gcc 288
 Glu Ala Ala Ala Val Asp Pro Gln Gln Arg Leu Ala Leu Glu Leu Ala
 85 90 95

tgg gag gca ctc gaa gac gcc ggt atc ccc gcc ggc gag ctg cgc ggt 336
 Trp Glu Ala Leu Glu Asp Ala Gly Ile Pro Ala Gly Glu Leu Arg Gly
 100 105 110

act gcc gcc ggt gtg ttc atg ggg gcg atc tct gac gac tac gcc gcc 384

Thr Ala Ala Gly Val Phe Met Gly Ala Ile Ser Asp Asp Tyr Ala Ala
 115 120 125

ctg ctg cgc gag agc ccg ccg gaa gtg gct gcg cag tac cgc ctc acc 432
 Leu Leu Arg Glu Ser Pro Pro Glu Val Ala Ala Gln Tyr Arg Leu Thr
 130 135 140

ggc acc cat cga agc ctg atc gcc aac cgc gtg tcc tat gtg ctc ggc 480
 Gly Thr His Arg Ser Leu Ile Ala Asn Arg Val Ser Tyr Val Leu Gly
 145 150 155 160

ctg cgc ggg cca agc ctg acg gtg gat tca ggt cag tcc tcc tcc ctg 528
 Leu Arg Gly Pro Ser Leu Thr Val Asp Ser Gly Gln Ser Ser Ser Leu
 165 170 175

gtc ggc gtg cat ctc gcc agc gag agc ctg cga cgg ggt gag tgc acg 576
 Val Gly Val His Leu Ala Ser Glu Ser Leu Arg Arg Gly Glu Cys Thr
 180 185 190

atc gca ctc gcc ggc ggc gtg aac ctc aac ctg gcc gcc gag agc aac 624
 Ile Ala Leu Ala Gly Gly Val Asn Leu Asn Leu Ala Ala Glu Ser Asn
 195 200 205

agc gct ctg atg gac ttc ggc gcg ctc tcc ccg gac ggt cgc tgc ttc 672
 Ser Ala Leu Met Asp Phe Gly Ala Leu Ser Pro Asp Gly Arg Cys Phe
 210 215 220

acc ttc gat gtg cgg gcg aac ggt tac gtc cgt ggt gag ggc ggc ggc 720
 Thr Phe Asp Val Arg Ala Asn Gly Tyr Val Arg Gly Glu Gly Gly Gly
 225 230 235 240

ctt gtc gtg ctg aag aag gcc gat cag gcg cac gcc gat ggc gac cgg 768
 Leu Val Val Leu Lys Lys Ala Asp Gln Ala His Ala Asp Gly Asp Arg
 245 250 255

atc tac tgc ctc atc cgc ggc agc gcg gtc aac aac gat ggg ggc ggt 816
 Ile Tyr Cys Leu Ile Arg Gly Ser Ala Val Asn Asn Asp Gly Gly Gly
 260 265 270

gcc ggg ctc acc gtt ccg gcg gcg gac gcc cag gcg gag ctg ctg cgc 864
 Ala Gly Leu Thr Val Pro Ala Ala Asp Ala Gln Ala Glu Leu Leu Arg
 275 280 285

cag gca tac cgg aac gcg ggc gtc gac ccg gcc gcc gtg cag tat gtc 912
 Gln Ala Tyr Arg Asn Ala Gly Val Asp Pro Ala Ala Val Gln Tyr Val
 290 295 300

gag ctc cac ggc agc gcg acc agg gtc ggg gat ccc gtc gaa gca gca 960

Pro Lys Leu Leu Ala Gly Leu Lys Ala Leu Ala Asp Gly Asp Asp Ala	
500	510
ccc acg ctg tgc cac ggc gcg act tcc ggc gag cgg gca gcg gtc ttc	1584
Pro Thr Leu Cys His Gly Ala Thr Ser Gly Glu Arg Ala Ala Val Phe	
515	520 525
gtc ttt ccc gga cag ggc agc cag tgg atc ggg atg ggt agg cag ctg	1632
Val Phe Pro Gly Gln Gly Ser Gln Trp Ile Gly Met Gly Arg Gln Leu	
530	535 540
ctc gaa acc tcc gag gtt ttc gcg gcg tcg atg tcg gac tgc gcc gac	1680
Leu Glu Thr Ser Glu Val Phe Ala Ala Ser Met Ser Asp Cys Ala Asp	
545	550 555 560
gca ttg gcg ccg cac ctg gat tgg tcc ctg ctg gat gtg ctg cgc aac	1728
Ala Leu Ala Pro His Leu Asp Trp Ser Leu Leu Asp Val Leu Arg Asn	
565	570 575
gcg gcc ggc gct gcg cac ctt gac cac gac gat gtc gtc cag ccc gcg	1776
Ala Ala Gly Ala Ala His Leu Asp His Asp Asp Val Val Gln Pro Ala	
580	585 590
ctg ttc gcc atc atg gtc tcg ctc gcg gag ctc tgg cgt tcg tgg ggc	1824
Leu Phe Ala Ile Met Val Ser Leu Ala Glu Leu Trp Arg Ser Trp Gly	
595	600 605
gtg cgt ccg gtg gcg gtc gtc ggg cac tcg cag ggg gag atc gcg gcg	1872
Val Arg Pro Val Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala	
610	615 620
gcc tgc gtc gcc ggg gcc ctg tcc gtc cgc gat gcc gcc agg gtg gtg	1920
Ala Cys Val Ala Gly Ala Leu Ser Val Arg Asp Ala Ala Arg Val Val	
625	630 635 640
gcg gtg cgc agc agg ctt ctg acg gcg ctg gcc ggc agt ggc gcg atg	1968
Ala Val Arg Ser Arg Leu Leu Thr Ala Leu Ala Gly Ser Gly Ala Met	
645	650 655
gcc tcg ttg cag cat ccc gcc gaa gag gtg cgg caa atc ctg ttg ccc	2016
Ala Ser Leu Gln His Pro Ala Glu Glu Val Arg Gln Ile Leu Leu Pro	
660	665 670
tggtgcgatcggatcggcgtggcggggtgaacggaaggcgatcgatcgacc	2064
TrpArgAspArgIleGlyValAlaGlyValAsnGlyProSerSerThr	
675	680 685
ctggtgtcataggacgggagggcgatggcgaaatgctggccgagtgc	2112

Leu Val Ser Gly Asp Arg Glu Ala Met Ala Glu Leu Leu Ala Glu Cys
 690 695 700

gca gac cga gag ctc cgg atg cgc cgg att ccc gtt gaa tac gcc tcc 2160
 Ala Asp Arg Glu Leu Arg Met Arg Arg Ile Pro Val Glu Tyr Ala Ser
 705 710 715 720

cat tcg cct cac atc gag gtt gtc cgg gat gag ctg ctg ggg ctg ttg 2208
 His Ser Pro His Ile Glu Val Val Arg Asp Glu Leu Leu Gly Leu Leu
 725 730 735

gcg ccg gtc gaa ccc agg acg gga agc atc ccg atc tat tcg acg acg 2256
 Ala Pro Val Glu Pro Arg Thr Gly Ser Ile Pro Ile Tyr Ser Thr Thr
 740 745 750

acc ggg gac ctg ctg gac cgg ccg atg gac gcc gac tac tgg tac cgc 2304
 Thr Gly Asp Leu Leu Asp Arg Pro Met Asp Ala Asp Tyr Trp Tyr Arg
 755 760 765

aac ctt cgt caa ccg gtg ctg ttc gaa gcg gcc gtc gag gcc ctg ttg 2352
 Asn Leu Arg Gln Pro Val Leu Phe Glu Ala Ala Val Glu Ala Leu Leu
 770 775 780

aag cgg ggg tac gac gca ttc atc gag atc agc cca cac ccg gtg ctg 2400
 Lys Arg Gly Tyr Asp Ala Phe Ile Glu Ile Ser Pro His Pro Val Leu
 785 790 795 800

act gcg aac atc cag gaa acc gcc gtg cga gca ggg cgg gag gta gtg 2448
 Thr Ala Asn Ile Gln Glu Thr Ala Val Arg Ala Gly Arg Glu Val Val
 805 810 815

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 Ala Leu Gly Thr Leu Arg Arg Gly Glu Gly Gly Met Arg Gln Ala Leu
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acg tcg ctg gcc aga gca cac gta cac gga gtg gcc gcg gac tgg cac 2544
 Thr Ser Leu Ala Arg Ala His Val His Gly Val Ala Ala Asp Trp His
 835 840 845

gcg gtc ttc gcc ggt acc ggg gcg cag cgg gtc gac ctg ccg acg tac 2592
 Ala Val Phe Ala Gly Thr Gly Ala Gln Arg Val Asp Leu Pro Thr Tyr
 850 855 860

gcc ttt cag cga cag cgc tac tgg ctg gac gcg aag ctt ccc gac gtc 2640
 Ala Phe Gln Arg Gln Arg Tyr Trp Leu Asp Ala Lys Leu Pro Asp Val
 865 870 875 880

gcc atg ccc gag agc gac gtg tcg acg gcg ttg cgg gaa aag ctg cgg 2688

Ala Met Pro Glu Ser Asp Val Ser Thr Ala Leu Arg Glu Lys Leu Arg
 885 890 895

tct tcg ccg agg gcg gac gtg gac tcg acg acc ctc acg atg atc cgg 2736
 Ser Ser Pro Arg Ala Asp Val Asp Ser Thr Thr Leu Thr Met Ile Arg
 900 905 910

gca cag gca gcc gtg gtc ctc ggc cac tcc gat ccg aaa gag gtg gac 2784
 Ala Gln Ala Ala Val Val Leu Gly His Ser Asp Pro Lys Glu Val Asp
 915 920 925

ccg gat ccg acg ttc aag gac ctg ggc ttc gat tcc tcg atg gtg gtc 2832
 Pro Asp Arg Thr Phe Lys Asp Leu Gly Phe Asp Ser Ser Met Val Val
 930 935 940

gag ctg tgc gac cgc cta aac gcc gcc aca ggt ctg cga ctc gca ccg 2880
 Glu Leu Cys Asp Arg Leu Asn Ala Ala Thr Gly Leu Arg Leu Ala Pro
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 995 1000 1005

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 Phe Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Gln Leu Val Ala
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 Ala Gly Arg Asp Val Val Ser Glu Phe Pro Ala Asp Arg Gly Trp Asp
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ctg gag cgt gcg ggg aca tcg cac gtg cgc gcc ggc ggg ttc ttg cat 3168
 Leu Glu Arg Ala Gly Thr Ser His Val Arg Ala Gly Gly Phe Leu His
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ggc gcc ccg gat ttt gac ccc ggg ttc ttc ccg att tcg ccg cgc gag 3216
 Gly Ala Pro Asp Phe Asp Pro Gly Phe Phe Arg Ile Ser Pro Arg Glu
 1060 1065 1070

gcg ttg gcg atg gat cca cag cag ccg ttg ctg ctg gaa atc gcc tgg 3264

Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Ile Ala Trp
 1075 1080 1085

gaa gca gtc gaa cga ggc ggg atc aac ccg cag cac ctg cac gga agt 3312
 Glu Ala Val Glu Arg Gly Gly Ile Asn Pro Gln His Leu His Gly Ser
 1090 1095 1100

caa acc ggg gtc ttc gtc ggc gcg acc tcc ctg gac tac ggg cca cgc 3360
 Gln Thr Gly Val Phe Val Gly Ala Thr Ser Leu Asp Tyr Gly Pro Arg
 1105 1110 1115 1120

ctg cac gaa gcg tcc gag gag gcg gcc ggg tac gtg ctc acc ggc agc 3408
 Leu His Glu Ala Ser Glu Glu Ala Ala Gly Tyr Val Leu Thr Gly Ser
 1125 1130 1135

acc acg agt gtg gcg tcg ggt cgg gtt gcg tat tcg ttc ggg ttc gag 3456
 Thr Thr Ser Val Ala Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu
 1140 1145 1150

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 Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala
 1155 1160 1165

ctg cat ttg gcg tgt cag tcg ttg cgt tcg ggt gag tgt gat ctg gcg 3552
 Leu His Leu Ala Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala
 1170 1175 1180

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 Leu Ala Gly Gly Val Thr Val Met Ala Thr Pro Gly Met Phe Val Glu
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 Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe
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gcg gag gcc gcc gac ggc acc ggc tgg tcc gag ggt gct ggc ctg gtt 3696
 Ala Glu Ala Ala Asp Gly Thr Gly Trp Ser Glu Gly Ala Gly Leu Val
 1220 1225 1230

cta ctg gag cgg ttg tcg gat gcc cgg cgg aat ggg cat gag gtg ctg 3744
 Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly His Glu Val Leu
 1235 1240 1245

gcg gtt gtt cgt ggt agt gcg gtg aat cag gac ggt gcg tcg aat ggt 3792
 Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly
 1250 1255 1260

ttg acc gcg ccg aat ggt tcg tcg cag cag ccg gtg att gcc cag gca 3840

Leu Thr Ala Pro A	ly Ser Ser Gln Gln Arg Val	Ile Ala Gln Ala	
1265	1270	1275	1280
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Leu Ala Ser Ala Gly Leu Ser Val Ser Asp Val Asp Ala Val Glu Ala			
1285	1290	1295	
cat ggg acg ggc acg cgg ctt ggt gat ccg atc gag gcg cag gcg ctg			3936
His Gly Thr Gly Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu			
1300	1305	1310	
atc gcc acc tac ggc cag ggc cgg ctt ccg gaa cgg cca ttg tgg ttg			3984
Ile Ala Thr Tyr Gly Gln Gly Arg Leu Pro Glu Arg Pro Leu Trp Leu			
1315	1320	1325	
ggc tcg atg aag tcg aac atc ggt cac gcg cag gca gct gcg ggg ata			4032
Gly Ser Met Lys Ser Asn Ile Gly His Ala Gln Ala Ala Ala Gly Ile			
1330	1335	1340	
gcc ggc gtc atg aag atg gtg atg gcg atg cgg cac ggg cag cta ccg			4080
Ala Gly Val Met Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro			
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Arg Thr Leu His Val Asp Glu Pro Thr Ser Gly Val Asp Trp Ser Ala			
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Gly Thr Val Gln Leu Leu Thr Glu Asn Thr Pro Trp Pro Gly Ser Gly			
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Arg Val Arg Arg Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn			
1395	1400	1405	
gcg cac gtc atc ctc gaa cag ccc ccg gga gtg ccg agt cag tct gcg			4272
Ala His Val Ile Leu Glu Gln Pro Pro Gly Val Pro Ser Gln Ser Ala			
1410	1415	1420	
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Gly Pro Gly Ser Gly Ser Val Val Asp Val Pro Val Val Pro Trp Met			
1425	1430	1435	1440
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Val Ser Gly Lys Thr Pro Glu Ala Leu Ser Ala Gln Ala Thr Ala Leu			
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atg acc tat ctg gac gag cga cct gat gtc tcc tcg ctg gat gtt ggg			4416

Met Thr Tyr Leu Asp Glu Arg Pro Asp Val Ser Ser Leu Asp Val Gly
 1460 1465 1470

tac tcg ctg gcg ttg aca cgg tcg gcg ctg gat gag cga gcg gtg gtg 4464
 Tyr Ser Leu Ala Leu Thr Arg Ser Ala Leu Asp Glu Arg Ala Val Val
 1475 1480 1485

ctg ggg tcg gac cgt gaa acg ttg ttg tgc ggt gtg aaa gcg ctg tct 4512
 Leu Gly Ser Asp Arg Glu Thr Leu Leu Cys Gly Val Lys Ala Leu Ser
 1490 1495 1500

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 1505 1510 1515 1520

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atg ggc cgg ggg ctt tac cgg gct ttt ccg gtg ttc gct gct gcc ttt 4656
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 Val Arg Glu Val Val Ser Gly Ser Asp Ala Gln Leu Leu Asp Arg Thr
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 Leu Trp Ala Gln Ser Gly Leu Phe Ala Leu Gln Val Gly Leu Leu Lys
 1585 1590 1595 1600

ttg ctg gat tcg tgg ggg gtt cgg ccg agt gtg gtg ttg ggg cat tcg 4848
 Leu Leu Asp Ser Trp Gly Val Arg Pro Ser Val Val Leu Gly His Ser
 1605 1610 1615

gtg ggc gag ttg gcg gcg gcg ttc gcg gcg ggt gtg gtg tcg ttg tcg 4896
 Val Gly Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Val Ser Leu Ser
 1620 1625 1630

ggt gcg gct cgg ttg gtg gcg ggt cgt gcc cgg ttg atg cag gcg ttg 4944
 Gly Ala Ala Arg Leu Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu
 1635 1640 1645

ccg tct ggc ggt ggg atg ctg gcg gtg cct gct ggt gag gag ctg ttg 4992

His Val Arg Gly Gly Ala Val Asp Trp Arg Ser Phe Phe Ala Gly Thr	
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agg gcg aag caa atc gag ctg ccc acc tac gcc ttc caa cga cag cgg	5616
Arg Ala Lys Gln Ile Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln Arg	
1860 1865 1870	
tac tgg ctg aac gcg ctg cgt gaa tct tcc gcc ggc gac atg ggc agg	5664
Tyr Trp Leu Asn Ala Leu Arg Glu Ser Ser Ala Gly Asp Met Gly Arg	
1875 1880 1885	
cgt gtc gaa gcg aag ttc tgg ggc gcc gtc gag cac gaa gat gtg gaa	5712
Arg Val Glu Ala Lys Phe Trp Gly Ala Val Glu His Glu Asp Val Glu	
1890 1895 1900	
tcg ctt gca cgc gta ttg ggc att gtg gac gac ggc gct gct gtg gat	5760
Ser Leu Ala Arg Val Leu Gly Ile Val Asp Asp Gly Ala Ala Val Asp	
1905 1910 1915 1920	
tcc ctg aga agc gcc ctt ccg gtg ttg gcc ggt tgg cag cga acc cgc	5808
Ser Leu Arg Ser Ala Leu Pro Val Leu Ala Gly Trp Gln Arg Thr Arg	
1925 1930 1935	
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Thr Thr Glu Ser Ile Met Asp Gln Arg Cys Tyr Arg Ile Gly Trp Arg	
1940 1945 1950	
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Gln Val Ala Gly Leu Pro Pro Met Gly Thr Val Phe Gly Thr Trp Leu	
1955 1960 1965	
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Val Phe Ala Pro His Gly Trp Ser Ser Glu Pro Glu Val Val Asp Cys	
1970 1975 1980	
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Val Thr Ala Leu Arg Ala Arg Gly Ala Ser Val Val Leu Val Glu Ala	
1985 1990 1995 2000	
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Asp Pro Asp Pro Thr Ser Phe Gly Asp Arg Val Arg Thr Leu Cys Ser	
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Gly Leu Pro Asp Leu Val Gly Val Leu Ser Met Leu Cys Leu Glu Glu	
2020 2025 2030	
tcg gtc ctt ccg gga ttt tct gcg gtg tca cgg ggt ttt gcg ttg acc	6144

Ser Val Leu Pro G	Phe Ser Ala Val Ser Arg Gly P	Ala Leu Thr	
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Val Glu Leu Val Arg Val Leu Arg Ala Ala Gly Ala Thr Ala Arg Leu			
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Trp Leu Leu Thr Cys Gly Gly Val Ser Val Gly Asp Val Pro Val Arg			
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cca gcg cag gcc ctg gcg tgg ggg ttg ggg cgt gtt gtg ggg ttg gag			6288
Pro Ala Gln Ala Leu Ala Trp Gly Leu Gly Arg Val Val Gly Leu Glu			
2085	2090	2095	
cat ccg gac tgg tgg ggc ggc ttg atc gat att ccg gtc ttg ttc gac			6336
His Pro Asp Trp Trp Gly Gly Leu Ile Asp Ile Pro Val Leu Phe Asp			
2100	2105	2110	
gaa gac gct caa gag cgg ttg tgc att gtg ctg gca ggt ctc gat gag			6384
Glu Asp Ala Gln Glu Arg Leu Ser Ile Val Leu Ala Gly Leu Asp Glu			
2115	2120	2125	
gac gag gtc gcg atc cgt cct gac ggc atg ttc gcg cgt cgg ttg gta			6432
Asp Glu Val Ala Ile Arg Pro Asp Gly Met Phe Ala Arg Arg Leu Val			
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cgc cac act gtc tca gct gat gtg aag aag gcg tgg cgc ccc agg gga			6480
Arg His Thr Val Ser Ala Asp Val Lys Lys Ala Trp Arg Pro Arg Gly			
2145	2150	2155	2160
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Ser Val Leu Val Thr Gly Gly Thr Gly Gly Leu Gly Ala His Val Ala			
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Arg Trp Leu Ala Asp Ala Gly Ala Glu His Val Ala Met Val Ser Arg			
2180	2185	2190	
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Arg Gly Glu Gln Ala Pro Ser Ala Glu Lys Leu Arg Thr Glu Leu Glu			
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Asp Leu Gly Thr Arg Val Ser Ile Val Ser Cys Asp Val Thr Asp Arg			
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Glu Ala Leu Ala Glu Val Leu Lys Ala Leu Pro Ala Glu Asn Pro Leu
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acc gcg gta gtg cat gcg gca ggc gtg atc gag act ggt gat gcg gcg 6768
 Thr Ala Val Val His Ala Ala Gly Val Ile Glu Thr Gly Asp Ala Ala
 2245 2250 2255

gca atg agc ctg gct gat ttc gat cac gtg ttg tcc gca aag gtg gcc 6816
 Ala Met Ser Leu Ala Asp Phe Asp His Val Leu Ser Ala Lys Val Ala
 2260 2265 2270

ggt gcc gcg aat ctg gat gcc ttg ttg gcc gat gtg gaa ttg gac gcg 6864
 Gly Ala Ala Asn Leu Asp Ala Leu Leu Ala Asp Val Glu Leu Asp Ala
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 Phe Val Leu Phe Ser Ser Val Ser Gly Val Trp Gly Ala Gly Gly His
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 Gly Ala Tyr Ala Ala Ala Asn Ala Tyr Leu Asp Ala Leu Ala Glu Gln
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Ser Ala Ala Pro Arg Pro Thr Gln Glu Gln Leu Ile Leu Glu Leu Val			
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Arg Glu Ser			
2595			

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Gly Thr Asp Ala Ile Thr Thr Val Pro Glu Gly Arg Trp Gly Asp Pro
35 40 45

Leu Pro Gly Arg Asp Ala Pro Lys Gly Pro Glu Trp Gly Gly Phe Leu
50 55 60

Ala Asp Val Asp Cys Phe Asp Pro Glu Phe Phe Gly Ile Ser Pro Arg
65 70 75 80

Glu Ala Ala Ala Val Asp Pro Gln Gln Arg Leu Ala Leu Glu Leu Ala
85 90 95

Trp Glu Ala Leu Glu Asp Ala Gly Ile Pro Ala Gly Glu Leu Arg Gly
100 105 110

Thr Ala Ala Gly Val Phe Met Gly Ala Ile Ser Asp Asp Tyr Ala Ala
115 120 125

Leu Leu Arg Glu Ser Pro Pro Glu Val Ala Ala Gln Tyr Arg Leu Thr
130 135 140

Gly Thr His Arg Ser Leu Ile Ala Asn Arg Val Ser Tyr Val Leu Gly
145 150 155 160

Leu Arg Gly Pro Ser Leu Thr Val Asp Ser Gly Gln Ser Ser Ser Leu
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Val Gly Val His Leu Ala Ser Glu Ser Leu Arg Arg Gly Glu Cys Thr
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Ile Ala Leu Ala Gly Gly Val Asn Leu Asn Leu Ala Ala Glu Ser Asn
195 200 205

Ser Ala Leu Met Asp Phe Gly Ala Leu Ser Pro Asp Gly Arg Cys Phe
210 215 220

Thr Phe Asp Val Ala Asn Gly Tyr Val Arg Gly Gly Gly Gly
225 230 235 240

Leu Val Val Leu Lys Lys Ala Asp Gln Ala His Ala Asp Gly Asp Arg
245 250 255

Ile Tyr Cys Leu Ile Arg Gly Ser Ala Val Asn Asn Asp Gly Gly Gly
260 265 270

Ala Gly Leu Thr Val Pro Ala Ala Asp Ala Gln Ala Glu Leu Leu Arg
275 280 285

Gln Ala Tyr Arg Asn Ala Gly Val Asp Pro Ala Ala Val Gln Tyr Val
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Glu Leu His Gly Ser Ala Thr Arg Val Gly Asp Pro Val Glu Ala Ala
305 310 315 320

Ala Leu Gly Ala Val Leu Gly Ala Ala Arg Arg Pro Gly Asp Glu Leu
325 330 335

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Gly Val Thr Gly Leu Leu Lys Thr Ala Leu Ser Ile Trp His Arg Glu
355 360 365

Leu Pro Pro Ser Leu His Phe Thr Ala Pro Asn Pro Glu Ile Pro Leu
370 375 380

Asp Glu Leu Asn Leu Arg Val Gln Arg Asp Leu Arg Pro Trp Pro Glu
385 390 395 400

Ser Glu Gly Pro Leu Leu Ala Gly Val Ser Ala Phe Gly Met Gly Gly
405 410 415

Thr Asn Cys His Leu Val Leu Ser Gly Thr Ser Arg Val Glu Arg Arg
420 425 430

Arg Ser Gly Pro Ala Glu Ala Thr Met Pro Trp Val Leu Ser Ala Arg
435 440 445

Thr Pro Val Ala Leu Arg Ala Gln Ala Ala Arg Leu His Thr His Leu
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Asn Thr Ala Gly Gln Ser Pro Leu Asp Val Ala Tyr Ser Leu Ala Thr
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Thr Arg Ser Ala Leu Pro His Arg Ala Ala Leu Val Ala Asp Asp Glu
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Pro Lys Leu Leu Ala Gly Leu Lys Ala Leu Ala Asp Gly Asp Asp Ala
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gga cga aca gcg gat gtc ccg gag acg act ccg cat gca ctc gac ctg 3888
 Gly Arg Thr Ala Asp Val Arg Glu Thr Thr Arg His Ala Leu Asp Leu
 1285 1290 1295

gta caa ggc tgg ctt tcc gat cag cga ctc aac gaa tcc cga ttg ctc -3936
 Val Gln Gly Trp Leu Ser Asp Gln Arg Leu Asn Glu Ser Arg Leu Leu
 1300 1305 1310

ctg gtg aca cag gga gca gtg gcc gtg gag ccg ggc gaa ccc gtg acc 3984
 Leu Val Thr Gln Gly Ala Val Ala Val Glu Pro Gly Glu Pro Val Thr
 1315 1320 1325

gat ctg gcg cag gcc gcg ctc tgg gga ctg ctg ccg tcg acg cag acc 4032
 Asp Leu Ala Gln Ala Ala Leu Trp Gly Leu Leu Arg Ser Thr Gln Thr
 1330 1335 1340

gaa cac cct gat cgc ttc gtc ctc gtc gat gtg cct gag ccc gcg caa 4080
 Glu His Pro Asp Arg Phe Val Leu Val Asp Val Pro Glu Pro Ala Gln
 1345 1350 1355 1360

ctc ctc ccc gcg ctg ccg ggg gtg ctg gcc tgc ggc gaa cct cag ctc 4128
 Leu Leu Pro Ala Leu Pro Gly Val Leu Ala Cys Gly Glu Pro Gln Leu
 1365 1370 1375

gcg ttg cga cgt ggc ggc gct cat gcg ccc aga ctg gct gga ctg ggc 4176
 Ala Leu Arg Arg Gly Gly Ala His Ala Pro Arg Leu Ala Gly Leu Gly
 1380 1385 1390

agc gat gac gtc ctg ccc gtg ccg gac ggc acc ggg tgg cga ttg gag 4224
 Ser Asp Asp Val Leu Pro Val Pro Asp Gly Thr Gly Trp Arg Leu Glu
 1395 1400 1405

gcc acg cgc ccg gga agc ctg gat ggg ttg gca ttg gtg gac gaa ccg 4272
 Ala Thr Arg Pro Gly Ser Leu Asp Gly Leu Ala Leu Val Asp Glu Pro
 1410 1415 1420

acg gcc acg gca ccg ctg ggt gac ggt gag gtc agg att gcg atg cgc 4320
 Thr Ala Thr Ala Pro Leu Gly Asp Gly Glu Val Arg Ile Ala Met Arg
 1425 1430 1435 1440

gcg gcc ggg gtg aac ttc cgg gat gcg ctc atc gcg ctc ggt atg tat 4368
 Ala Ala Gly Val Asn Phe Arg Asp Ala Leu Ile Ala Leu Gly Met Tyr
 1445 1450 1455

ccc ggt gtg gca tcg ctg ggc agt gag ggc gcc ggg gtc gtg gtg gag 4416
 Pro Gly Val Ala Ser Leu Gly Ser Glu Gly Ala Gly Val Val Val Glu
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acc ggc ccc ggc gtc acc ggc ctg gca ccc ggc gac cgc gtg atg gga 4464
 Thr Gly Pro Gly Val Thr Gly Leu Ala Pro Gly Asp Arg Val Met Gly
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gtg atc ccg aag gcg ttc ggg ccg ctc gcg gtc gcc gac cat cgc atg 4512
 Met Ile Pro Lys Ala Phe Gly Pro Leu Ala Val Ala Asp His Arg Met
 1490 1495 1500

gtg acg agg att ccc gct ggt tgg agc ttc gcg cgg gcc gca tcg gtg 4560
 Val Thr Arg Ile Pro Ala Gly Trp Ser Phe Ala Arg Ala Ala Ser Val
 1505 1510 1515 1520

ccg atc gtc ttt ctc acc gcc tac tac gcg ctg gtt gat ctc gcc ggg 4608
 Pro Ile Val Phe Leu Thr Ala Tyr Tyr Ala Leu Val Asp Leu Ala Gly
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 Leu Arg Pro Gly Glu Ser Leu Leu Val His Ser Ala Ala Gly Gly Val
 1540 1545 1550

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 Gly Met Ala Ala Ile Gln Leu Ala Arg His Leu Gly Ala Glu Val Tyr
 1555 1560 1565

gcc acc gct agc gag gac aag tgg caa gcc gtg gag ctg agc cga gaa 4752
 Ala Thr Ala Ser Glu Asp Lys Trp Gln Ala Val Glu Leu Ser Arg Glu
 1570 1575 1580

cac ctc gct tcg tcg cgg acg tgc gat ttc gag cag cag ttc ctc ggg 4800
 His Leu Ala Ser Ser Arg Thr Cys Asp Phe Glu Gln Gln Phe Leu Gly
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gca acc ggc gga cgc ggc gtc gac gtc gtg ctc aac tcc ctc gcc ggg 4848
 Ala Thr Gly Gly Arg Gly Val Asp Val Val Leu Asn Ser Leu Ala Gly
 1605 1610 1615

gag ttc gcc gat g	ct ctg cga atg ctg ccg cgc ggc cgt ttc	4896
Glu Phe Ala Asp Ala Ser Leu Arg Met Leu Pro Arg Gly Gly Arg Phe		
1620	1625	1630
ctg gag ttg ggg aag acg gat gtt cgt gac ccc gtc gag gtc gcc gat	4944	
Leu Glu Leu Gly Lys Thr Asp Val Arg Asp Pro Val Glu Val Ala Asp		
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gcg cat ccg ggc gtg tct tac cag gct ttc gat acc gta gag gca ggc	4992	
Ala His Pro Gly Val Ser Tyr Gln Ala Phe Asp Thr Val Glu Ala Gly		
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ccg cag cga atc ggc gag atg ctt cac gag ctg gtg gag ttg ttc gag	5040	
Pro Gln Arg Ile Gly Glu Met Leu His Glu Leu Val Glu Leu Phe Glu		
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gga cgc gtg ctg gag ccc ctg cct gtc acg gct tgg gac gtt cgg cag	5088	
Gly Arg Val Leu Glu Pro Leu Pro Val Thr Ala Trp Asp Val Arg Gln		
1685	1690	1695
gcg ccc gag gcg cta cgg cac ctg agc caa gcg cgg cat gtg gga aag	5136	
Ala Pro Glu Ala Leu Arg His Leu Ser Gln Ala Arg His Val Gly Lys		
1700	1705	1710
ctg gtg ctc acc atg cct ccg gtg tgg gac gcc gca ggc acg gtt ctg	5184	
Leu Val Leu Thr Met Pro Pro Val Trp Asp Ala Ala Gly Thr Val Leu		
1715	1720	1725
gtt acc ggc gga acg gga gca ctt ggc gca gag gtc gcc cgg cac ctc	5232	
Val Thr Gly Gly Thr Gly Ala Leu Gly Ala Glu Val Ala Arg His Leu		
1730	1735	1740
gtg atc gag cgc ggg gtg cga aac ctg gtc ctc gtc agc agg cgc ggt	5280	
Val Ile Glu Arg Gly Val Arg Asn Leu Val Leu Val Ser Arg Arg Gly		
1745	1750	1755
ccc gca gcc agt ggc gct gct gag ctc gtg gcg caa ctg acg gcc tac	5328	
Pro Ala Ala Ser Gly Ala Ala Glu Leu Val Ala Gln Leu Thr Ala Tyr		
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ggt gcc gag gtt tcc ttg cag gct tgc gat gtc gcc gat cgt gag acc	5376	
Gly Ala Glu Val Ser Leu Gln Ala Cys Asp Val Ala Asp Arg Glu Thr		
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ttg gcg aag gtg ctt gcc agc atc ccg gac gag cat ccg ttg acc gcc	5424	
Leu Ala Lys Val Leu Ala Ser Ile Pro Asp Glu His Pro Leu Thr Ala		
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gtg gtg cac gcg gct ggt gtt ctc gac gac gga gtg tcc gaa tcg ctc	5472
Val Val His Ala Ala Gly Val Leu Asp Asp Gly Val Ser Glu Ser Leu	
1810 1815 1820	
acc gtg gag cgg ctg gac cag gtt ctg cgc ccg aag gtc gat ggc gcg	5520
Thr Val Glu Arg Leu Asp Gln Val Leu Arg Pro Lys Val Asp Gly Ala	
1825 1830 1835 1840	
cgg aat ctg ctc gag ctg atc gac ccg gac gtg gcc ctc gtg ttg ttc	5568
Arg Asn Leu Leu Glu Leu Ile Asp Pro Asp Val Ala Leu Val Leu Phe	
1845 1850 1855	
tcg tcg gtg tcg ggt gtg ctc ggc agc ggt ggg cag ggt aac tac gcg	5616
Ser Ser Val Ser Gly Val Leu Gly Ser Gly Gly Gln Gly Asn Tyr Ala	
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gcg gcc aac tcc ttc ctc gac gca ttg gcg cag caa agg cag tcg cgc	5664
Ala Ala Asn Ser Phe Leu Asp Ala Leu Ala Gln Gln Arg Gln Ser Arg	
1875 1880 1885	
ggc cta ccg acg aga tca ttg gcc tgg ggg ccc tgg gcg gaa cat ggc	5712
Gly Leu Pro Thr Arg Ser Leu Ala Trp Gly Pro Trp Ala Glu His Gly	
1890 1895 1900	
atg gcc agc acc ttg cgc gaa gcc gag cag gat cga ttg gcg cga tct	5760
Met Ala Ser Thr Leu Arg Glu Ala Glu Gln Asp Arg Leu Ala Arg Ser	
1905 1910 1915 1920	
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1925 1930 1935	
gcg tgc ggc ggc gcg cat acc gtg gtg gcg ccg gtt cga ttc agc cgc	5856
Ala Cys Gly Gly Ala His Thr Val Val Ala Pro Val Arg Phe Ser Arg	
1940 1945 1950	
ttg tcc gac ggg aac gcg atc aag ttc tcc gtc ctg caa ggt ttg gtc	5904
Leu Ser Asp Gly Asn Ala Ile Lys Phe Ser Val Leu Gln Gly Leu Val	
1955 1960 1965	
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Gly Pro His Arg Val Asn Lys Ala Ala Thr Ala Asp Asp Ala Glu Ser	
1970 1975 1980	
ctc cgg aaa cgg ttg gga cgc ttg ccg gat gca gaa caa cat cgg att	6000
Leu Arg Lys Arg Leu Gly Arg Leu Pro Asp Ala Glu Gln His Arg Ile	
1985 1990 1995 2000	

ctg ctg gac ctc ggc atg cat gtg gcg gca gtg ccca gga ttc gcc 6048
 Leu Leu Asp Leu Val Arg Met His Val Ala Ala Val Leu Gly Phe Ala
 2005 2010 2015

ggt tct cag gag atc acc gcg gac ggc acg ttc aag gtg ctg ggc ttc 6096
 Gly Ser Gln Glu Ile Thr Ala Asp Gly Thr Phe Lys Val Leu Gly Phe
 2020 2025 2030

gac tcg ttg acc gtg gtc gag ttg cgc aac cgg atc aac ggg gcg acg 6144
 Asp Ser Leu Thr Val Val Glu Leu Arg Asn Arg Ile Asn Gly Ala Thr
 2035 2040 2045

ggg ctg cga ctg ccc gcc acc ctg gtg ttc aac tac ccg acg ccg gat 6192
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 2050 2055 2060

gcg ctc gcc gcg cac ctc gtc acc gcg ctg tcc gca gac cgc ctg gcc 6240
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 2065 2070 2075 2080

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 Gly Thr Phe Glu Glu Leu Asp Arg Trp Ala Ala Asn Leu Pro Thr Leu
 2085 2090 2095

gcc agg gat gag gcc acg cgg gcg cag atc acc acc cgg cta cag gcg 6336
 Ala Arg Asp Glu Ala Thr Arg Ala Gln Ile Thr Thr Arg Leu Gln Ala
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 Ile Leu Gln Ser Leu Ala Asp Val Ser Gly Gly Thr Gly Gly Gly Ser
 2115 2120 2125

gtg ccg gac cgg ctc aga tcg gcc acg gac gac gag ctt ttc caa ctc 6432
 Val Pro Asp Arg Leu Arg Ser Ala Thr Asp Asp Glu Leu Phe Gln Leu
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35 40 45

Pro Gly Gln Val Ser Ser Pro Glu Asp Leu Trp Gln Leu Ala Ala Gly
50 55 60

Gly Val Asp Ala Ile Ser Glu Val Pro Gly Asp Arg Gly Trp Asp Leu
65 70 75 80

Asp Gly Val Phe Val Pro Asp Ser Asp Arg Pro Gly Thr Ser Tyr Ala
85 90 95

Lys Ala Gly Gly Phe Leu Gln Gly Val Ser Glu Phe Asp Ala Gly Phe
100 105 110

Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
115 120 125

Leu Leu Leu Glu Val Ala Trp Glu Val Phe Glu Arg Ala Gly Leu Glu
130 135 140

Gln Arg Ser Thr Arg Gly Ser Arg Val Gly Val Phe Val Gly Thr Asn
145 150 155 160

Gly Gln Asp Tyr Ala Ser Trp Leu Arg Thr Pro Pro Pro Ala Val Ala
165 170 175

Gly His Val Leu Thr Gly Gly Ala Ala Ala Val Leu Ser Gly Arg Val
180 185 190

Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala
195 200 205

Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu Arg
210 215 220

Ala Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser
225 230 235 240

Thr Pro Lys Val Phe Leu Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro
245 250 255

Asp Gly Arg Cys Lys Ser Phe Ala Ala Gly Ala Asp Gly Thr Gly Trp

260

265

270

Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg
 275 280 285

Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val Asn
 290 295 300

Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Ser Ser Gln
 305 310 315 320

Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val Ser
 325 330 335

Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp
 340 345 350

Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg Asp
 355 360 365

Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His
 370 375 380

Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala
 385 390 395 400

Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Glu Ser Pro Ser
 405 410 415

Pro Glu Val Asp Trp Ser Ala Gly Thr Val Gln Leu Leu Thr Glu Asn
 420 425 430

Thr Pro Trp Pro Arg Ser Gly Arg Val Arg Arg Val Gly Val Ser Ser
 435 440 445

Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Pro Pro
 450 455 460

Gly Val Pro Ser Gln Ser Ala Gly Pro Gly Ser Gly Ser Val Val Asp
 465 470 475 480

Val Pro Val Val Pro Trp Met Val Ser Gly Lys Thr Pro Glu Ala Leu
 485 490 495

Ser Ala Gln Ala Thr Ala Leu Met Thr Tyr Leu Asp Glu Arg Pro Asp
 500 505 510

Val Ser Ser Leu Asp Val Gly Tyr Ser Leu Ala Leu Thr Arg Ser Ala

515

520

525

Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Glu Thr Leu Leu
 530 535 540

Cys Gly Val Lys Ala Leu Ser Ala Gly His Glu Ala Ser Gly Leu Val
 545 550 555 560

Thr Gly Ser Val Gly Ala Gly Gly Arg Ile Gly Phe Val Phe Ser Gly
 565 570 575

Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu Tyr Arg Ala Phe
 580 585 590

Pro Val Phe Ala Ala Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp Ala
 595 600 605

His Leu Gly Gln Glu Ile Gly Val Arg Glu Val Val Ser Gly Ser Asp
 610 615 620

Ala Gln Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser Gly Leu Phe Ala
 625 630 635 640

Leu Gln Val Gly Leu Leu Lys Leu Leu Asp Ser Trp Gly Val Arg Pro
 645 650 655

Ser Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe Ala
 660 665 670

Ala Gly Val Val Ser Leu Ser Gly Ala Ala Arg Leu Val Ala Gly Arg
 675 680 685

Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Gly Met Leu Ala Val
 690 695 700

Pro Ala Gly Glu Glu Leu Leu Trp Ser Leu Leu Ala Asp Gln Gly Asp
 705 710 715 720

Arg Val Gly Ile Ala Ala Val Asn Ala Ala Gly Ser Val Val Leu Ser
 725 730 735

Gly Asp Arg Asp Val Leu Asp Asp Leu Ala Gly Arg Leu Asp Gly Gln
 740 745 750

Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser Tyr
 755 760 765

Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Thr Val

770

775

780

Asp Tyr Arg Arg Cys Glu Val Pro Ile Val Ser Thr Leu Thr Gly Asp
 785 790 795 800

Leu Asp Asp Ala Gly Arg Met Ser Gly Pro Asp Tyr Trp Val Arg Gln
 805 810 815

Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val Glu
 820 825 830

His Asp Val Ala Thr Val Val Glu Leu Gly Pro Asp Gly Ala Leu Ser
 835 840 845

Ala Leu Ile Gln Glu Cys Val Ala Ala Ser Asp His Ala Gly Arg Leu
 850 855 860

er Ala Val Pro Ala Met Arg Arg Asn Gln Asp Glu Ala Gln Lys Val
 865 870 875 880

Met Thr Ala Leu Ala His Val His Val Arg Gly Gly Ala Val Asp Trp
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Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Ile Glu Leu Pro Thr
 900 905 910

Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Val Pro Ser Asp Ser Gly
 915 920 925

Asp Val Thr Gly Ala Gly Leu Ala Gly Ala Glu His Pro Leu Leu Gly
 930 935 940

Ala Val Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg
 945 950 955 960

Ile Ser Val Arg Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly
 965 970 975

Glu Val Ile Val Ala Gly Thr Ala Leu Leu Glu Ile Ala Leu His Ala
 980 985 990

Gly Glu Arg Leu Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala
 995 1000 1005

Pro Leu Val Leu Pro Glu Arg Gly Ala Ile Gln Val Gln Leu Arg Val
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Gly Ala Pro Glu Asn Ser Gly Arg Arg Pro Met Ala Leu Tyr Ser Arg

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 Thr Glu Asp Ser Gly Phe Gly Val His Pro Ala Leu Leu Asp Ala Ala
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 Arg Leu Tyr Arg Leu Ser Trp Pro Thr Val Gln Leu Pro Thr Ser Ala
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12

1290

1295

Val Gln Gly Trp Leu Ser Asp Gln Arg Leu Asn Glu Ser Arg Leu Leu
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Leu Val Thr Gln Gly Ala Val Ala Val Glu Pro Gly Glu Pro Val Thr
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Asp Leu Ala Gln Ala Ala Leu Trp Gly Leu Leu Arg Ser Thr Gln Thr
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Glu His Pro Asp Arg Phe Val Leu Val Asp Val Pro Glu Pro Ala Gln
1345 1350 1355 1360

Leu Leu Pro Ala Leu Pro Gly Val Leu Ala Cys Gly Glu Pro Gln Leu
1365 1370 1375

la Leu Arg Arg Gly Gly Ala His Ala Pro Arg Leu Ala Gly Leu Gly
1380 1385 1390

Ser Asp Asp Val Leu Pro Val Pro Asp Gly Thr Gly Trp Arg Leu Glu
1395 1400 1405

Ala Thr Arg Pro Gly Ser Leu Asp Gly Leu Ala Leu Val Asp Glu Pro
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Thr Ala Thr Ala Pro Leu Gly Asp Gly Glu Val Arg Ile Ala Met Arg
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Ala Ala Gly Val Asn Phe Arg Asp Ala Leu Ile Ala Leu Gly Met Tyr
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Pro Gly Val Ala Ser Leu Gly Ser Glu Gly Ala Gly Val Val Val Glu
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Met Ile Pro Lys Ala Phe Gly Pro Leu Ala Val Ala Asp His Arg Met
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Val Thr Arg Ile Pro Ala Gly Trp Ser Phe Ala Arg Ala Ala Ser Val
1505 1510 1515 1520

Pro Ile Val Phe Leu Thr Ala Tyr Tyr Ala Leu Val Asp Leu Ala Gly
1525 1530 1535

Leu Arg Pro Gly Glu Ser Leu Leu Val His Ser Ala Ala Gly Gly Val

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Glu Phe Ala Asp Ala Ser Leu Arg Met Leu Pro Arg Gly Gly Arg Phe		
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Pro Ala Ala Ser Gly Ala Ala Glu Leu Val Ala Gln Leu Thr Ala Tyr		
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Gly Ala Glu Val Ser Leu Gln Ala Cys Asp Val Ala Asp Arg Glu Thr		
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1795

1800

1805

Val Val His Ala Ala Gly Val Leu Asp Asp Gly Val Ser Glu Ser Leu
1810 1815 1820

Thr Val Glu Arg Leu Asp Gln Val Leu Arg Pro Lys Val Asp Gly Ala
825 1830 1835 1840

Arg Asn Leu Leu Glu Leu Ile Asp Pro Asp Val Ala Leu Val Leu Phe
1845 1850 1855

Ser Ser Val Ser Gly Val Leu Gly Ser Gly Gly Gln Gly Asn Tyr Ala
1860 1865 1870

Ala Ala Asn Ser Phe Leu Asp Ala Leu Ala Gln Gln Arg Gln Ser Arg
1875 1880 1885

Gly Leu Pro Thr Arg Ser Leu Ala Trp Gly Pro Trp Ala Glu His Gly
1890 1895 1900

Met Ala Ser Thr Leu Arg Glu Ala Glu Gln Asp Arg Leu Ala Arg Ser
905 1910 1915 1920

Gly Leu Leu Pro Ile Ser Thr Glu Glu Gly Leu Ser Gln Phe Asp Ala
1925 1930 1935

Ala Cys Gly Gly Ala His Thr Val Val Ala Pro Val Arg Phe Ser Arg
1940 1945 1950

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1955 1960 1965

Gly Pro His Arg Val Asn Lys Ala Ala Thr Ala Asp Asp Ala Glu Ser
1970 1975 1980

Leu Arg Lys Arg Leu Gly Arg Leu Pro Asp Ala Glu Gln His Arg Ile
985 1990 1995 2000

Leu Leu Asp Leu Val Arg Met His Val Ala Ala Val Leu Gly Phe Ala
2005 2010 2015

Gly Ser Gln Glu Ile Thr Ala Asp Gly Thr Phe Lys Val Leu Gly Phe
2020 2025 2030

Asp Ser Leu Thr Val Val Glu Leu Arg Asn Arg Ile Asn Gly Ala Thr
2035 2040 2045

Gly Leu Arg Leu Pro Ala Thr Leu Val Phe Asn Tyr Pro Thr Pro Asp

2050

2055

2060

Ala Leu Ala Ala His Leu Val Thr Ala Leu Ser Ala Asp Arg Leu Ala
065 2070 2075 2080

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2085 2090 2095

Ala Arg Asp Glu Ala Thr Arg Ala Gln Ile Thr Thr Arg Leu Gln Ala
2100 2105 2110

Ile Leu Gln Ser Leu Ala Asp Val Ser Gly Gly Thr Gly Gly Gly Ser
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Asp Leu His Gln Ala Arg Glu Arg Leu His Glu Ala Glu Ser Gly Glu
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cgg gaa ccc atc gcg atc gtg gcg atg ggc tgc cgg tac ccg ggt ggg 144
Arg Glu Pro Ile Ala Ile Val Ala Met Gly Cys Arg Tyr Pro Gly Gly
35 40 45

gtg cag gac ccg gaa ggg ctg tgg aaa ctg gtc gcc tcc ggt ggc gac 192
Val Gln Asp Pro Glu Gly Leu Trp Lys Leu Val Ala Ser Gly Gly Asp
50 55 60

gcc atc ggt gaa ttc ccc gct gat cgt ggt tgg cac ctg gac gag ctc 240
 Ala Ile Gly Glu Phe Pro Ala Asp Arg Gly Trp His Leu Asp Glu Leu
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 Tyr Asp Pro Asp Pro Asp Gln Pro Gly Thr Cys Tyr Thr Arg His Gly
 85 90 95

ggc ttc ctc cac gac gcc ggc gag ttc gac gcg gga ttc ttc gac atc 336
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 100 105 110

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 115 120 125

gaa atc tcc tgg gag acc gtc gaa tcc gct ggg atg gac ccg agg tcc 432
 Glu Ile Ser Trp Glu Thr Val Glu Ser Ala Gly Met Asp Pro Arg Ser
 130 135 140

ttg ccg ggg agc cgc acc ggg gtg ttc gcg gga ttg atg tac gag ggc 480
 Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met Tyr Glu Gly
 145 150 155 160

tat gac acc ggc gcc cac ccg gca gga gaa ggt gtc gaa ggc tat ctc 528
 Tyr Asp Thr Gly Ala His Arg Ala Gly Glu Gly Val Glu Gly Tyr Leu
 165 170 175

gga acc ggc aat gcg gga agc gtc gcc tct ggt ccg gtt gcg tat gcg 576
 Gly Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Ala
 180 185 190

ttc ggg ttc gag ggc cca gcg gtg acg gta gac acg gcg tgc tcg tcg 624
 Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser
 195 200 205

tcg ttg gtg gcg ctg cat ttg gcg tgt cag tcg ttg ccg cag ggc gag 672
 Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Gln Gly Glu
 210 215 220

tgt gat ctg gcg ctg gcc ggt gga gtg acg gtg atg tcg acg ccg gag 720
 Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser Thr Pro Glu
 225 230 235 240

agg ttc gtg gag ttc tcc cgt cag cgt ggt ctc gca ccg gat ggg ccg 768
 Arg Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg
 245 250 255

tgt aag tcg ttc gcg gcg gct gcg gat gga acc ggt tgg ggt gag ggt 816
 Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
 260 265 270

gcc ggt ttg gtg ttg ctg gag cgg ctg tca gac gcc agg cgg aac ggg 864
 Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly
 275 280 285

cat cgg gta ctg gcg gtt gtt cgt ggt agc gcg gtg aat cag gac ggt 912
 His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly
 290 295 300

gcg tcg aac gga ttg acg gcc ccg aac ggg ctg gcc cag gag cgg gtc 960
 Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu Ala Gln Glu Arg Val
 305 310 315 320

ttc cag cag gtg ctc acg agt gcg ggg ctg tcg gcg tcc gat gtg gac 1008
 Ile Gln Gln Val Leu Thr Ser Ala Gly Leu Ser Ala Ser Asp Val Asp
 325 330 335

gct gtg gag gcg cat gga acg ggt acg cgg ctt ggt gat ccg atc gag 1056
 Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp Pro Ile Glu
 340 345 350

gcg cag gct ctg ata gcc gcc tat gga cag gat cgg gac cgg gac cgg 1104
 Ala Gln Ala Leu Ile Ala Ala Tyr Gly Gln Asp Arg Asp Arg Asp Arg
 355 360 365

ccg ctg tgg ttg ggg tcg gtc aag tcc aac atc ggt cat acg cag gcg 1152
 Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His Thr Gln Ala
 370 375 380

gct gcg ggc gtc gct ggt gtg atc aag atg gtc atg gcg atg cgg cac 1200
 Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala Met Arg His
 385 390 395 400

ggg gag ctg ccg cgc acg ttg cac gtg gac gag ccg aat tcg cac gtg 1248
 Gly Glu Leu Pro Arg Thr Leu His Val Asp Glu Pro Asn Ser His Val
 405 410 415

gac tgg tcg gct ggt gcg gtc cga ctc ctg acc gag aac atc cgc tgg 1296
 Asp Trp Ser Ala Gly Ala Val Arg Leu Leu Thr Glu Asn Ile Arg Trp
 420 425 430

cca ggg acg ggt acg cgc cgc gct gga gtg tcg tcg ttc ggg gta agc 1344
 Pro Gly Thr Gly Thr Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser
 435 440 445

ggt acc aac gca cac gtc atc ctc gaa cac gac ccg ctc gcc gtg acc	1392
Gly Thr Asn Ala His Val Ile Leu Glu His Asp Pro Leu Ala Val Thr	
450 455 460	
gag aac gag gaa gca gcg cag tcc cca gca cct ggg atc gtg ccc tgg	1440
Glu Asn Glu Glu Ala Ala Gln Ser Pro Ala Pro Gly Ile Val Pro Trp	
465 470 475 480	
gcg ttg tcc ggg cgg tcg tcg acg gcg ctg cgg gcc cag gcc gaa cgg	1488
Ala Leu Ser Gly Arg Ser Ser Thr Ala Leu Arg Ala Gln Ala Glu Arg	
485 490 495	
ctg cgc gag ctg tgc gag cag acc gat ccc gac ccc gtc gat gtc ggt	1536
Leu Arg Glu Leu Cys Glu Gln Thr Asp Pro Asp Pro Val Asp Val Gly	
500 505 510	
tca ctg gcc gcc acg cgc acg gct tgg gag cac cga gcg gtg gtg	1584
Phe Ser Leu Ala Ala Thr Arg Thr Ala Trp Glu His Arg Ala Val Val	
515 520 525	
ctt ggt cgg gac agc gct acg ttg cgc tcc ggg ctt ggc gtt gtt gcc	1632
Leu Gly Arg Asp Ser Ala Thr Leu Arg Ser Gly Leu Gly Val Val Ala	
530 535 540	
agc ggt gaa cca gcg gtc gat gtc gtt gag ggg agc gtc ctg gac ggc	1680
Ser Gly Glu Pro Ala Val Asp Val Val Glu Gly Ser Val Leu Asp Gly	
545 550 555 560	
gag gtc gtc ttc gtc ttc ccc ggt cag ggc tgg cag tgg gcc ggt atg	1728
Glu Val Val Phe Val Phe Pro Gly Gln Gly Trp Gln Trp Ala Gly Met	
565 570 575	
gca gtc gac ctg ctg gac gct tcg ccg acg ttc gcg cgc cac atg gac	1776
Ala Val Asp Leu Leu Asp Ala Ser Pro Thr Phe Ala Arg His Met Asp	
580 585 590	
gag tgc gcc acc gcg ctg cgg agg tac gtg gac tgg tcg ttg gtc gac	1824
Glu Cys Ala Thr Ala Leu Arg Arg Tyr Val Asp Trp Ser Leu Val Asp	
595 600 605	
gtg ctg cgc gga gcg gag aac tcc cca ccg ctg gac cgg gtg gac gtg	1872
Val Leu Arg Gly Ala Glu Asn Ser Pro Pro Leu Asp Arg Val Asp Val	
610 615 620	
ctc cag ccc gcg tcc ttc gcg gtg atg gtg tcg ctc gcc gag gtg tgg	1920
Leu Gln Pro Ala Ser Phe Ala Val Met Val Ser Leu Ala Glu Val Trp	
625 630 635 640	

cgt tcc tac ggg gtg agg ccg gcg gcc gtc gtc ggc cac agt caa ggc	1968
Arg Ser Tyr Gly Val Arg Pro Ala Ala Val Val Gly His Ser Gln Gly	
645 650 655	
gaa atc gcc gcg gcc tgc gca gcc ggg gtg ctg ccg ctg gag gat gcg	2016
Glu Ile Ala Ala Ala Cys Ala Ala Gly Val Leu Pro Leu Glu Asp Ala	
660 665 670	
gcc agg ctt gtc gca ttg cgc agc aga gcg ttg aag gga ctt tcg ggg	2064
Ala Arg Leu Val Ala Leu Arg Ser Arg Ala Leu Lys Gly Leu Ser Gly	
675 680 685	
cgg ggt ggc atg gcg tcg ctg gcc tgc cct gcg gat gag gtc gcg gca	2112
Arg Gly Gly Met Ala Ser Leu Ala Cys Pro Ala Asp Glu Val Ala Ala	
690 695 700	
ctg ttc gcg gga tcg ggc ggc cgt ctg gaa gtt gcg gcg atc aac ggc	2160
Leu Phe Ala Gly Ser Gly Gly Arg Leu Glu Val Ala Ala Ile Asn Gly	
705 710 715 720	
ccg cga tcg gtc gtg gtg tcc ggc gat ctg gaa gcg gtg gac gaa ctg	2208
Pro Arg Ser Val Val Val Ser Gly Asp Leu Glu Ala Val Asp Glu Leu	
725 730 735	
ctg gca gag tgc gct gaa aag gac atg cgt gca cgc cgt atc ccc gtc	2256
Leu Ala Glu Cys Ala Glu Lys Asp Met Arg Ala Arg Arg Ile Pro Val	
740 745 750	
gac tac gcc tcg cat tca gcg cac gtg gag gtg gtt cgg agc ccg gtg	2304
Asp Tyr Ala Ser His Ser Ala His Val Glu Val Val Arg Ser Pro Val	
755 760 765	
ctg gcg gcc gcc gcc ggg gtg cga cac cgg gac ggc cag gtg ccg tgg	2352
Leu Ala Ala Ala Ala Gly Val Arg His Arg Asp Gly Gln Val Pro Trp	
770 775 780	
tgg tcg acg gtg atc ggc gac tgg gtg gat ccg gcc agg ctg gac ggc	2400
Trp Ser Thr Val Ile Gly Asp Trp Val Asp Pro Ala Arg Leu Asp Gly	
785 790 795 800	
gag tat tgg tat cgg aac ctc cgg cag ccg gtc cgg ttc gaa cac gcc	2448
Glu Tyr Trp Tyr Arg Asn Leu Arg Gln Pro Val Arg Phe Glu His Ala	
805 810 815	
gtg cag ggc ctg gtc gag cgg gga ttc ggc ctg ttc atc gaa atg agt	2496
Val Gln Gly Leu Val Glu Arg Gly Phe Gly Leu Phe Ile Glu Met Ser	
820 825 830	

gcg cat ccg gtg ctg acc acg gcg gtc gag gaa acc ggt gcg gag tcg	2544
Ala His Pro Val Leu Thr Thr Ala Val Glu Glu Thr Gly Ala Glu Ser	
835 840 845	
gag acc gcc gtg gcc gcg gta ggt acc ttg cga cgt gac tcg ggc ggc	2592
Glu Thr Ala Val Ala Ala Val Gly Thr Leu Arg Arg Asp Ser Gly Gly	
850 855 860	
ctc cgg agg ttg ttg cat tcg ctg gcc gag gcg tac gtg cgc ggc gcc	2640
Leu Arg Arg Leu Leu His Ser Leu Ala Glu Ala Tyr Val Arg Gly Ala	
865 870 875 880	
acc gtg gac tgg gcc gtg gcg ttc ggg ggc gcg ggc cga cgg ctg gac	2688
Thr Val Asp Trp Ala Val Ala Phe Gly Gly Ala Gly Arg Arg Leu Asp	
885 890 895	
ctg ccg acc tac ccg ttc cag cgc cag cgg tac tgg ctg gac aag gga	2736
Leu Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Asp Lys Gly	
900 905 910	
gct gcc tcc gac gag gct cgt gcg gtc tcg gac ccg gcg gcg ggc tgg	2784
Ala Ala Ser Asp Glu Ala Arg Ala Val Ser Asp Pro Ala Ala Gly Trp	
915 920 925	
ttc tgg caa gcc gtg gcg cgc caa gac ctg aaa agc gtg tcc gat gcc	2832
Phe Trp Gln Ala Val Ala Arg Gln Asp Leu Lys Ser Val Ser Asp Ala	
930 935 940	
ctc gat ctc gac gcc gac gca ccg ctg agc gca aca ctt cca gcc ctg	2880
Leu Asp Leu Asp Ala Asp Ala Pro Leu Ser Ala Thr Leu Pro Ala Leu	
945 950 955 960	
tcc gtc tgg cac cgt cag gaa cga gaa agg gtc ttg gca gac ggt tgg	2928
Ser Val Trp His Arg Gln Glu Arg Glu Arg Val Leu Ala Asp Gly Trp	
965 970 975	
cgg tac cga gtc gac tgg gta cgg gtg gcc ccg cag ccg gtc cgg aga	2976
Arg Tyr Arg Val Asp Trp Val Arg Val Ala Pro Gln Pro Val Arg Arg	
980 985 990	
acg cgg gaa acc tgg ctc ctg gtc gtt ccc ccg ggc ggc atc gag gaa	3024
Thr Arg Glu Thr Trp Leu Leu Val Val Pro Pro Gly Gly Ile Glu Glu	
995 1000 1005	
gcg ctg gtc gaa cgg ctg acg gat gcg ttg aac acg cga ggg atc agc	3072
Ala Leu Val Glu Arg Leu Thr Asp Ala Leu Asn Thr Arg Gly Ile Ser	
1010 1015 1020	

acc ctg cgc ctc gac gtg cca ccg gcg gcg acc agt ggc gaa ctc gca	3120
Thr Leu Arg Leu Asp Val Pro Pro Ala Ala Thr Ser Gly Glu Leu Ala	
1025 1030 1035 1040	
acc gaa ctc cgc gcc gca gcc gac ggt gac ccg gtg aag gca atc ctg	3168
Thr Glu Leu Arg Ala Ala Ala Asp Gly Asp Pro Val Lys Ala Ile Leu	
1045 1050 1055	
tcg ctc acc gcg ttg gac gag cga ccc cac ccc gaa tgc aag gac gtc	3216
Ser Leu Thr Ala Leu Asp Glu Arg Pro His Pro Glu Cys Lys Asp Val	
1060 1065 1070	
ccg agc ggg att gcc ttg ctg ctg aac ctg gtc aag gcg ctc ggt gaa	3264
Pro Ser Gly Ile Ala Leu Leu Leu Asn Leu Val Lys Ala Leu Gly Glu	
1075 1080 1085	
acc gac ctc aga att cct ctg tgg acc atc acg cgt ggt gcg gtc aag	3312
Ala Asp Leu Arg Ile Pro Leu Trp Thr Ile Thr Arg Gly Ala Val Lys	
1090 1095 1100	
gca ggc ccc gca gat cgg ctg ctg cgc ccg atg cag gcg caa gca tgg	3360
Ala Gly Pro Ala Asp Arg Leu Leu Arg Pro Met Gln Ala Gln Ala Trp	
1105 1110 1115 1120	
ggt ctg ggg cga gta gcc gca ctc gaa cac ccc gag cgc tgg ggt ggg	3408
Gly Leu Gly Arg Val Ala Ala Leu Glu His Pro Glu Arg Trp Gly Gly	
1125 1130 1135	
ctg atc gac ctg ccg gat tcg ctg gac ggc gac gtc ctc acg agg ctg	3456
Leu Ile Asp Leu Pro Asp Ser Leu Asp Gly Asp Val Leu Thr Arg Leu	
1140 1145 1150	
ggc gaa gcg ctc acc aac ggc ttg gcg gaa gac caa ctg gcg att cgc	3504
Gly Glu Ala Leu Thr Asn Gly Leu Ala Glu Asp Gln Leu Ala Ile Arg	
1155 1160 1165	
cag tcg ggc gtg ctg gcc ccg cga ctg gta ccc gcc ccg gcg aat cag	3552
Gln Ser Gly Val Leu Ala Arg Arg Leu Val Pro Ala Pro Ala Asn Gln	
1170 1175 1180	
ccc gct gga cgt aag tgg cgc ccc cga ggg agc gcg ctg atc acg ggc	3600
Pro Ala Gly Arg Lys Trp Arg Pro Arg Gly Ser Ala Leu Ile Thr Gly	
1185 1190 1195 1200	
gga ctc ggc gcg gtg ggc gca cag gtg gcg agg tgg ttg gcc gaa atc	3648
Gly Leu Gly Ala Val Gly Ala Gln Val Ala Arg Trp Leu Ala Glu Ile	
1205 1210 1215	

gga gcc gag cga atc gtg ctc acc agt cga cgg ggc aac caa gca gca Gly Ala Glu Arg Ile Val Leu Thr Ser Arg Arg Gly Asn Gln Ala Ala 1220 1225 1230	3696
ggc gcc gcc gag ctg gaa gcc gaa ctc cgg gcc ctt gga gcg caa gtg Gly Ala Ala Glu Leu Glu Ala Glu Leu Arg Ala Leu Gly Ala Gln Val 1235 1240 1245	3744
tcc atc gtg gct tgc gac gtg acc gat cgt gcc gag atg tcc gca cta Ser Ile Val Ala Cys Asp Val Thr Asp Arg Ala Glu Met Ser Ala Leu 1250 1255 1260	3792
ctg gcc gag ttc gac gtc acc gcg gtg ttc cac gcg gcc gga gtc ggt Leu Ala Glu Phe Asp Val Thr Ala Val Phe His Ala Ala Gly Val Gly 1265 1270 1275 1280	3840
ggc ctg ctg ccg ttg gcg gag acc gac cag aac ggc ctg gcc gaa ata Arg Leu Leu Pro Leu Ala Glu Thr Asp Gln Asn Gly Leu Ala Glu Ile 1285 1290 1295	3888
tgc gcg gcg aag gtc cgc ggc gct cag gtg ctg gac gaa ctg tgc gac Cys Ala Ala Lys Val Arg Gly Ala Gln Val Leu Asp Glu Leu Cys Asp 1300 1305 1310	3936
agc acc gat ctc gat gcc ttc gtc ctg ttc tcc tcg ggt gcc ggg gta Ser Thr Asp Leu Asp Ala Phe Val Leu Phe Ser Ser Gly Ala Gly Val 1315 1320 1325	3984
tgg ggc ggg ggc ggt cag ggc gct tac ggc gcg gcg aac gca ttc ttg Trp Gly Gly Gly Gly Gln Gly Ala Tyr Gly Ala Ala Asn Ala Phe Leu 1330 1335 1340	4032
gac aca ctc gcc gaa caa cgc cga gca cgc ggt ctg ccg gca acc tcg Asp Thr Leu Ala Glu Gln Arg Arg Ala Arg Gly Leu Pro Ala Thr Ser 1345 1350 1355 1360	4080
atc tcc tgg ggc agt tgg gcc ggc ggc ggc atg gcc gac ggc gcg gcg Ile Ser Trp Gly Ser Trp Ala Gly Gly Gly Met Ala Asp Gly Ala Ala 1365 1370 1375	4128
ggc gaa cac ctg cgg cga cgc ggg ata cgt ccg atg ccg gcg gcg tcg Gly Glu His Leu Arg Arg Arg Gly Ile Arg Pro Met Pro Ala Ala Ser 1380 1385 1390	4176
gcc atc ctg gct ctg cag gaa gta ctt gac cag gat gag acg tgc gtg Ala Ile Leu Ala Leu Gln Glu Val Leu Asp Gln Asp Glu Thr Cys Val 1395 1400 1405	4224

tcg atc gct gat gtg gac tgg gac cga ttc gtt ccc acg ttc gcc gcg	4272
Ser Ile Ala Asp Val Asp Trp Asp Arg Phe Val Pro Thr Phe Ala Ala	
1410 1415 1420	
act cgc gcc acc cgg ttg ttc gac gaa gtg ccg gcg gcg aga aag gcg	4320
Thr Arg Ala Thr Arg Leu Phe Asp Glu Val Pro Ala Ala Arg Lys Ala	
1425 1430 1435 1440	
atg ccc gcg aat ggg ccg gca gaa cca ggc ggc tcg ccg ttc gcc cgc	4368
Met Pro Ala Asn Gly Pro Ala Glu Pro Gly Gly Ser Pro Phe Ala Arg	
1445 1450 1455	
aat ctc gcg gag ctg ccg gaa gcc caa cga cgc cac gaa ctg gtg gat	4416
Asn Leu Ala Glu Leu Pro Glu Ala Gln Arg Arg His Glu Leu Val Asp	
1460 1465 1470	
gtg gtg tgc gcc cag gtg gca acc gtg ctc ggg cac ggc agt cgc gag	4464
Leu Val Cys Ala Gln Val Ala Thr Val Leu Gly His Gly Ser Arg Glu	
1475 1480 1485	
gaa gtc cag ccc gag cgg gcg ttc cgc gcg ctc ggg ttc gac tcc ctc	4512
Glu Val Gln Pro Glu Arg Ala Phe Arg Ala Leu Gly Phe Asp Ser Leu	
1490 1495 1500	
atg gcg gtg gat ctg cgc aat cgt ttg acc acc gcc acc ggg ttg cgc	4560
Met Ala Val Asp Leu Arg Asn Arg Leu Thr Thr Ala Thr Gly Leu Arg	
1505 1510 1515 1520	
ctg ccg acc aca acc gtc ttc gac tac ccg aat ccg gcc gcc ttg gcc	4608
Leu Pro Thr Thr Thr Val Phe Asp Tyr Pro Asn Pro Ala Ala Leu Ala	
1525 1530 1535	
gct cac ctg ctc gag gag ctg gtg ggt gat gtc gcg tcg gct gcg gtg	4656
Ala His Leu Leu Glu Glu Leu Val Gly Asp Val Ala Ser Ala Ala Val	
1540 1545 1550	
acc gct gcc agc gcg ccc gcg agt gac gaa ccg atc gcg atc gtc gcg	4704
Thr Ala Ala Ser Ala Pro Ala Ser Asp Glu Pro Ile Ala Ile Val Ala	
1555 1560 1565	
atg agc tgc cgg ttt ccg ggt ggc gcg cac tcg ccg gaa gac ctg tgg	4752
Met Ser Cys Arg Phe Pro Gly Gly Ala His Ser Pro Glu Asp Leu Trp	
1570 1575 1580	
cgg ctg gtc gcc gcc ggc acg gag gtg atc ggc gag ttc ccc tcc gac	4800
Arg Leu Val Ala Ala Gly Thr Glu Val Ile Gly Glu Phe Pro Ser Asp	
1585 1590 1595 1600	

cgg ggc tgg gat gcg gaa ggc ctt tac gat ccg gat gct tcc agg cct	4848
Arg Gly Trp Asp Ala Glu Gly Leu Tyr Asp Pro Asp Ala Ser Arg Pro	
1605 1610 1615	
gga acg acg tat gcg cgg atg gcg gga ttc ctc tac gac gcc ggt gag	4896
Gly Thr Thr Tyr Ala Arg Met Ala Gly Phe Leu Tyr Asp Ala Gly Glu	
1620 1625 1630	
ttc gat gcc gac ctg ttc ggc atc agc cca cgt gag gcg ttg gcg atg	4944
Phe Asp Ala Asp Leu Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met	
1635 1640 1645	
gat ccg cag cag cgg ttg gtg ctc gaa atc gcc tgg gaa gcc ctc gaa	4992
Asp Pro Gln Gln Arg Leu Val Leu Glu Ile Ala Trp Glu Ala Leu Glu	
1650 1655 1660	
cgg gcc gga atc gat ccg ttg tcc ttg aag ggc agt ggg gtc ggc acg	5040
Arg Ala Gly Ile Asp Pro Leu Ser Leu Lys Gly Ser Gly Val Gly Thr	
1665 1670 1675 1680	
tac atc ggc gct gga agc cgt ggg tac gcg acg gat gtg cgg cag ttt	5088
Tyr Ile Gly Ala Gly Ser Arg Gly Tyr Ala Thr Asp Val Arg Gln Phe	
1685 1690 1695	
ccc gag gag gcg gag ggc tac ctg ctg acg ggt acc tcg gcc agt gtg	5136
Pro Glu Glu Ala Glu Gly Tyr Leu Leu Thr Gly Thr Ser Ala Ser Val	
1700 1705 1710	
ctg tcg ggt cgg gtc gcg tat tcg ttt ggt ttc gag ggt cct gcg gtg	5184
Leu Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val	
1715 1720 1725	
acg gtg gat acg gct tgt tcg tcg tcg ttg gtg gcg ttg cat ctg gcg	5232
Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala	
1730 1735 1740	
tgc cag tcg ttg cgt tcg ggc gag tgt gat ctg gcg ttg gcc ggt ggt	5280
Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly	
1745 1750 1755 1760	
gtg acc gtg atg tcg acg ccg gag atg ttc gtg gag ttc tcc cgt cag	5328
Val Thr Val Met Ser Thr Pro Glu Met Phe Val Glu Phe Ser Arg Gln	
1765 1770 1775	
cgc ggt ttg gcg ccg gat ggg cgg tgc aag tcg ttc gcg gag agc gcg	5376
Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala	
1780 1785 1790	

gac ggc acc ggc tgg ggc gaa ggc gcg ggc ctg ttg ttg ctg gag cgg	5424
Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg	
1795 1800 1805	
ttg tcg gac gcc cac cgg aat ggg cat cgg gtg ttg gcg gtg gtt cgt	5472
Leu Ser Asp Ala His Arg Asn Gly His Arg Val Leu Ala Val Val Arg	
1810 1815 1820	
ggg tca gcg gtg aat cag gac ggc gcc tcg aac gga ctg gcg gcg ccg	5520
Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Ala Ala Pro	
1825 1830 1835 1840	
aac ggt ccg tcg cag cag cgg gtg atc aac cag gca ctc gcg aat gcg	5568
Asn Gly Pro Ser Gln Gln Arg Val Ile Asn Gln Ala Leu Ala Asn Ala	
1845 1850 1855	
ctt ctt tcg gcg tcc gat gtg gat gcg gtg gag gca cat ggc acc ggg	5616
Ala Leu Ser Ala Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly	
1860 1865 1870	
acc agg ctg ggt gat ccg atc gag gcg cag gca ttg atc gca acg tat	5664
Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr	
1875 1880 1885	
ggg cag gcc cgg gag cgg gat cgg ccc ttg tgg ctg ggg tcg gtc aag	5712
Gly Gln Ala Arg Glu Arg Asp Arg Pro Leu Trp Leu Gly Ser Val Lys	
1890 1895 1900	
tcg aac atc ggt cat acg cag gcc gcg gcg ggt gtt gcc ggt gtg atc	5760
Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile	
1905 1910 1915 1920	
aag atg gtg atg gcc atg cgg cac ggg cag ctg ccc gcc tcg ctg cac	5808
Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro Ala Ser Leu His	
1925 1930 1935	
gcg gat gag ccc acg tcg gag gtc gat tgg tcg tcg ggg gcg gtc cgg	5856
Ala Asp Glu Pro Thr Ser Glu Val Asp Trp Ser Ser Gly Ala Val Arg	
1940 1945 1950	
ctc ctc gcc gaa cag gta cct tgg ccg gag tct gac cgt gtt cgt cgg	5904
Leu Leu Ala Glu Gln Val Pro Trp Pro Glu Ser Asp Arg Val Arg Arg	
1955 1960 1965	
gtg ggg gtt tcg tcg ttc ggg atc agc ggc acc aac gca cat gtg atc	5952
Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile	
1970 1975 1980	

ctc gaa caa gct acg aat gcg cca gat agt aca gcg gag acg gac aaa 6000
 Leu Glu Gln Ala Thr Asn Ala Pro Asp Ser Thr Ala Glu Thr Asp Lys
 1985 1990 1995 2000

aca gaa tcc gga tct act gtc gat att ccg gtc gtt ccc tgg ttg gtg 6048
 Thr Glu Ser Gly Ser Thr Val Asp Ile Pro Val Val Pro Trp Leu Val
 2005 2010 2015

tcg gga aag acg acg gat tcc ctg cgg gga caa gcc gaa cga gtc ttg 6096
 Ser Gly Lys Thr Thr Asp Ser Leu Arg Gly Gln Ala Glu Arg Val Leu
 2020 2025 2030

tct cag gtc gag tcc cgg ccg gag cag cgt tcg ctg gat gtt gcc tac 6144
 Ser Gln Val Glu Ser Arg Pro Glu Gln Arg Ser Leu Asp Val Ala Tyr
 2035 2040 2045

tcg ctt gct tct ggc cga gcc gcg ctg gat gaa cgc gct gtc gtg ctg 6192
 Ser Leu Ala Ser Gly Arg Ala Ala Leu Asp Glu Arg Ala Val Val Leu
 2050 2055 2060

ggc ggc gac cgc ggt gag ctg gtt gct gga ctg gcg gcg ttg gcc gcc 6240
 Gly Ala Asp Arg Gly Glu Leu Val Ala Gly Leu Ala Ala Leu Ala Ala
 2065 2070 2075 2080

ggc cag gag gct tct ggg gtg atc agc gga act cgt gct tct gct cgg 6288
 Gly Gln Glu Ala Ser Gly Val Ile Ser Gly Thr Arg Ala Ser Ala Arg
 2085 2090 2095

ttc ggg ttc gtg ttc tcg ggg cag ggt ggt cag tgg ttg ggg atg ggc 6336
 Phe Gly Phe Val Phe Ser Gly Gln Gly Gly Gln Trp Leu Gly Met Gly
 2100 2105 2110

aga gcg ctc tac tcg aag ttt ccg gtg ttc gct gct gcg ttt gat gag 6384
 Arg Ala Leu Tyr Ser Lys Phe Pro Val Phe Ala Ala Ala Phe Asp Glu
 2115 2120 2125

gct tgc gcc gag ttg gag gca cat ctg ggg gaa gac cgc cgg gtt cgg 6432
 Ala Cys Ala Glu Leu Glu Ala His Leu Gly Glu Asp Arg Arg Val Arg
 2130 2135 2140

gat gtg gtc ttc ggt tcc gat gcg cag ctg ctg gat cag acg ctg tgg 6480
 Asp Val Val Phe Gly Ser Asp Ala Gln Leu Leu Asp Gln Thr Leu Trp
 2145 2150 2155 2160

gcg cag tcg ggt ctg ttc gcg ctg caa gcc ggc ctc ttg ggg ctg ctg 6528
 Ala Gln Ser Gly Leu Phe Ala Leu Gln Ala Gly Leu Leu Gly Leu Leu
 2165 2170 2175

ggt tcg tgg ggc gtt cgg ccg gat gtg gtg atg ggg cat tcg gtc ggg 6576
 Gly Ser Trp Gly Val Arg Pro Asp Val Val Met Gly His Ser Val Gly
 2180 2185 2190

gag ttg gcc gcc gcg ttt gcg gct ggc gtg ttg tcg ttg cgg gat gcg 6624
 Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Leu Ser Leu Arg Asp Ala
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gct cgg ttg gtg gcc gcg cgc gcc cgg ttg atg caa gcc ctg ccc tct 6672
 Ala Arg Leu Val Ala Ala Arg Ala Arg Leu Met Gln Ala Leu Pro Ser
 2210 2215 2220

gac ggc gcg atg ttg gcg gtg gct gct ggt gaa gac ctt gtt cgg cca 6720
 Asp Gly Ala Met Leu Ala Val Ala Ala Gly Glu Asp Leu Val Arg Pro
 2225 2230 2235 2240

gtg ctg gcc ggt cgg gag gag tcc gtg agc gtc gcc gcg ctc aat gcc 6768
 Leu Leu Ala Gly Arg Glu Glu Ser Val Ser Val Ala Ala Leu Asn Ala
 2245 2250 2255

ccc ggt tcg gtg gtg ttg tcg ggc gat cgg gag gtg ctg gcc agc atc 6816
 Pro Gly Ser Val Val Leu Ser Gly Asp Arg Glu Val Leu Ala Ser Ile
 2260 2265 2270

gtc ggc cgg ctg acc gag ctc cga gtc cgg acg cgg cgc ttg cgg gtc 6864
 Val Gly Arg Leu Thr Glu Leu Arg Val Arg Thr Arg Arg Leu Arg Val
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tcc cat gct ttt cat tcg cac cgg atg gac ccg atg ttg ggc gag ttc 6912
 Ser His Ala Phe His Ser His Arg Met Asp Pro Met Leu Gly Glu Phe
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 Val Ser Thr Leu Thr Gly Glu Leu Asp Arg Ala Ala Glu Met Ser Thr
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cca ggg tat tgg gtg cgc cag gcg cgt gaa ccc gtc cgt ttc gcc gac 7056
 Pro Gly Tyr Trp Val Arg Gln Ala Arg Glu Pro Val Arg Phe Ala Asp
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 Gly Val Gln Ala Leu Ala Ala Gln Gly Ile Gly Thr Val Val Glu Leu
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Gly Pro Asp Gly Thr Leu Ala Ala Leu Val Arg Glu Cys Ala Thr Glu	
2370 2375 2380	
tcc gat cgg gtt ggg cgg att tcg tcg atc cca ctg atg cgc agg gag	7200
Ser Asp Arg Val Gly Arg Ile Ser Ser Ile Pro Leu Met Arg Arg Glu	
2385 2390 2395 2400	
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Arg Asp Glu Thr Arg Ser Val Met Thr Ala Leu Ala His Leu His Thr	
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Arg Gly Gly Glu Val Asp Trp Gln Ala Phe Phe Ala Gly Thr Gly Ala	
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Arg Gln Leu Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln His Tyr Trp	
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atc gag tcc agt gcg cgg cca gca cgc gac cgc gca gac atc ggc gag	7392
Ile Glu Ser Ser Ala Arg Pro Ala Arg Asp Arg Ala Asp Ile Gly Glu	
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Val Ala Glu Gln Phe Trp Thr Ala Val Asp Gln Gly Asp Leu Ala Thr	
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ttg gtc gcc gct ctg gat ctt ggg gcg gac gac gac aca tgc gca tcg	7488
Leu Val Ala Ala Leu Asp Leu Gly Ala Asp Asp Asp Thr Cys Ala Ser	
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Leu Ser Asp Val Leu Pro Ala Leu Ser Ser Trp Arg Ser Gly Leu Arg	
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Asn Arg Ser Leu Val Asp Ser Cys Arg Tyr Arg Ile Ser Trp His Ser	
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Ser Arg Glu Val Pro Ala Pro Lys Ile Ser Gly Thr Trp Leu Leu Val	
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Val Pro Gly Ala Ala Asp Asp Gly Leu Val Thr Ala Leu Thr Ser Ser	
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Leu Val Gly Gly Gly Ala Glu Val Val Arg Ile Gly Leu Ser Glu Glu	
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Asp Pro His Arg Glu Asp Val Ala Gln Arg Leu Ala Asn Ala Leu Thr	
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Asp Ala Gly Gln Leu Gly Gly Val Leu Ser Leu Leu Gly Leu Asp Glu	
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Ser Pro Ala Pro Gly Phe Ser Cys Leu Pro Thr Gly Phe Ala Leu Thr	
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Val Gln Leu Leu Arg Ala Leu Arg Lys Ala Asp Val Glu Ala Pro Phe	
2625 2630 2635 2640	
tgg gcg gtg acg cgc ggc ggc gtc gcg ttg gaa gat gta cgc gtg tct	7968
Trp Ala Val Thr Arg Gly Gly Val Ala Leu Glu Asp Val Arg Val Ser	
2645 2650 2655	
ccg gag cag gcc ctg gtc tgg ggg ctg ctg cgt gtc gcg gga ctg gag	8016
Pro Glu Gln Ala Leu Val Trp Gly Leu Leu Arg Val Ala Gly Leu Glu	
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His Pro Glu Phe Trp Gly Gly Leu Ile Asp Leu Pro Ser Asp Trp Asp	
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Asp Arg Leu Gly Ala Arg Leu Ala Gly Val Leu Ala Asp Gly Gly Glu	
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Asp Gln Val Ala Ile Arg Arg Gly Gly Val Phe Val Arg Arg Leu Glu	
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Arg Ala Gly Ala Ser Gly Ala Gly Ser Val Trp Arg Pro Arg Gly Thr	
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Val Leu Val Thr Gly Gly Thr Gly Gly Leu Gly Ala His Val Ala Arg	
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Trp Leu Ala Gly Ala Gly Ala Glu His Val Val Leu Thr Ser Arg Arg	
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Gly Ala Asp Ala Pro Gly Ala Gly Glu Leu Arg Ala Glu Leu Glu Ala	
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Leu Gly Ala Arg Val Ser Ile Val Pro Cys Asp Val Ala Asp Arg Asp	
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cg gtg gta cac gcc gcc ggg gtc ggc gag gcg ggc gac gta gtg gag	8496
Ala Val Val His Ala Ala Gly Val Gly Glu Ala Gly Asp Val Val Glu	
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Met Gly Leu Ala Asp Phe Ala Ala Val Leu Ser Ala Lys Val Arg Gly	
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Val Met Phe Ser Ser Val Ser Gly Val Trp Gly Ala Gly Gly Gln Gly	
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Gly Asp Gly Met Ala Ala Gly Glu Thr Gly Ala Gln Leu His Arg Met	
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Gly Leu Ala Ser Met Glu Pro Ser Ala Ala Leu Leu Ala Leu Gln Gly	
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Asp Thr Ile Asp Glu Ala Arg Ala Ala Leu Glu Thr Thr Gly Glu Gln
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Ala Gly Thr Gly Lys Pro Val Glu Leu Thr Gln Arg Leu Ala Gly Leu
2995 3000 3005

cg cgg aag gaa cgc gac gat gcg gta ttg gat ctg gtg cgg gcg gag 9072
Ser Arg Lys Glu Arg Asp Asp Ala Val Leu Asp Leu Val Arg Ala Glu
3010 3015 3020

acg gcg gct gtg ctg gga cgc gac gat gcc acg gcc ctg gcg cca tcg 9120
Thr Ala Ala Val Leu Gly Arg Asp Asp Ala Thr Ala Leu Ala Pro Ser
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cgg ccg ttc cag gaa ctc gga ttc gac tcc ttg atg gcg gtg gag ctg 9168
 Arg Pro Phe Gln Glu Leu Gly Phe Asp Ser Leu Met Ala Val Glu Leu
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Arg Asn Arg Leu Asn Thr Ala Thr Gly Ile Gln Leu Pro Ala Ser Thr
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Ile Phe Asp Tyr Pro Asn Ala Glu Ser Leu Ser Arg His Leu Cys Ala
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gag ctt ttc cca acg gag act acc gtg gac tcg gcc ctt gcc gag ctc 9312
Glu Leu Phe Pro Thr Glu Thr Thr Val Asp Ser Ala Leu Ala Glu Leu
3090 3095 3100

gat cga atc gag cag cag ctc tcg atg ctc acc ggc gaa gcg cgg gca 9360
Asp Arg Ile Glu Gln Gln Leu Ser Met Leu Thr Gly Glu Ala Arg Ala
3105 3110 3115 3120

cgg gac cga atc gcg aca cga ctg cga gcc ctc cac gag aag tgg aac 9408
Arg Asp Arg Ile Ala Thr Arg Leu Arg Ala Leu His Glu Lys Trp Asn
3125 3130 3135

agc gca gct gaa gta ccg acc gga gcc gat gtc ctg agc acg ctc gat 9456
Ser Ala Ala Glu Val Pro Thr Gly Ala Asp Val Leu Ser Thr Leu Asp
3140 3145 3150

tcg gcg acg cac gac gag ata ttc gag ttc atc gac aac gag ctc gac 9504
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ctg tcc tga 9513
Leu Ser
3170

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<211> 3170

<212> PRT

<213> Saccharopolyspora spinosa

<400> 46

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Asp Leu His Gln Ala Arg Glu Arg Leu His Glu Ala Glu Ser Gly Glu
20 25 30

Arg Glu Pro Ile Ala Ile Val Ala Met Gly Cys Arg Tyr Pro Gly Gly
35 40 45

Val Gln Asp Pro Glu Gly Leu Trp Lys Leu Val Ala Ser Gly Gly Asp
50 55 60

Ala Ile Gly Glu Phe Pro Ala Asp Arg Gly Trp His Leu Asp Glu Leu
65 70 75 80

Tyr Asp Pro Asp Pro Asp Gln Pro Gly Thr Cys Tyr Thr Arg His Gly
85 90 95

Gly Phe Leu His Asp Ala Gly Glu Phe Asp Ala Gly Phe Phe Asp Ile
100 105 110

Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
115 120 125

Glu Ile Ser Trp Glu Thr Val Glu Ser Ala Gly Met Asp Pro Arg Ser
130 135 140

Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met Tyr Glu Gly

145		150		155		160
Tyr Asp Thr Gly Ala His Arg Ala Gly Glu Gly Val Glu Gly Tyr Leu						
	165		170		175	
Gly Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Ala						
	180		185		190	
Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser						
	195		200		205	
Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Gln Gly Glu						
	210		215		220	
Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser Thr Pro Glu						
	225		230		235	240
Arg Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg						
	245		250		255	
Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly						
	260		265		270	
Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly						
	275		280		285	
His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly						
	290		295		300	
Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu Ala Gln Glu Arg Val						
	305		310		315	320
Ile Gln Gln Val Leu Thr Ser Ala Gly Leu Ser Ala Ser Asp Val Asp						
	325		330		335	
Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp Pro Ile Glu						
	340		345		350	
Ala Gln Ala Leu Ile Ala Ala Tyr Gly Gln Asp Arg Asp Arg Asp Arg						
	355		360		365	
Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His Thr Gln Ala						
	370		375		380	
Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala Met Arg His						
	385		390		395	400
Gly Glu Leu Pro Arg Thr Leu His Val Asp Glu Pro Asn Ser His Val						

405

410

415

Asp Trp Ser Ala Gly Ala Val Arg Leu Leu Thr Glu Asn Ile Arg Trp
420 425 430

Pro Gly Thr Gly Thr Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser
435 440 445

Gly Thr Asn Ala His Val Ile Leu Glu His Asp Pro Leu Ala Val Thr
450 455 460

Glu Asn Glu Glu Ala Ala Gln Ser Pro Ala Pro Gly Ile Val Pro Trp
465 470 475 480

Ala Leu Ser Gly Arg Ser Ser Thr Ala Leu Arg Ala Gln Ala Glu Arg
485 490 495

Leu Arg Glu Leu Cys Glu Gln Thr Asp Pro Asp Pro Val Asp Val Gly
500 505 510

Phe Ser Leu Ala Ala Thr Arg Thr Ala Trp Glu His Arg Ala Val Val
515 520 525

Leu Gly Arg Asp Ser Ala Thr Leu Arg Ser Gly Leu Gly Val Val Ala
530 535 540

Ser Gly Glu Pro Ala Val Asp Val Val Glu Gly Ser Val Leu Asp Gly
545 550 555 560

Glu Val Val Phe Val Phe Pro Gly Gln Gly Trp Gln Trp Ala Gly Met
565 570 575

Ala Val Asp Leu Leu Asp Ala Ser Pro Thr Phe Ala Arg His Met Asp
580 585 590

Glu Cys Ala Thr Ala Leu Arg Arg Tyr Val Asp Trp Ser Leu Val Asp
595 600 605

Val Leu Arg Gly Ala Glu Asn Ser Pro Pro Leu Asp Arg Val Asp Val
610 615 620

Leu Gln Pro Ala Ser Phe Ala Val Met Val Ser Leu Ala Glu Val Trp
625 630 635 640

Arg Ser Tyr Gly Val Arg Pro Ala Ala Val Val Gly His Ser Gln Gly
645 650 655

Glu Ile Ala Ala Ala Cys Ala Ala Gly Val Leu Pro Leu Glu Asp Ala

660	665	670
Ala Arg Leu Val Ala Leu Arg Ser Arg Ala Leu Lys Gly Leu Ser Gly		
675	680	685
Arg Gly Gly Met Ala Ser Leu Ala Cys Pro Ala Asp Glu Val Ala Ala		
690	695	700
Leu Phe Ala Gly Ser Gly Gly Arg Leu Glu Val Ala Ala Ile Asn Gly		
705	710	715 720
Pro Arg Ser Val Val Val Ser Gly Asp Leu Glu Ala Val Asp Glu Leu		
	725	730 735
Leu Ala Glu Cys Ala Glu Lys Asp Met Arg Ala Arg Arg Ile Pro Val		
	740	745 750
Asp Tyr Ala Ser His Ser Ala His Val Glu Val Val Arg Ser Pro Val		
	755	760 765
Leu Ala Ala Ala Ala Gly Val Arg His Arg Asp Gly Gln Val Pro Trp		
	770	775 780
Trp Ser Thr Val Ile Gly Asp Trp Val Asp Pro Ala Arg Leu Asp Gly		
785	790	795 800
Glu Tyr Trp Tyr Arg Asn Leu Arg Gln Pro Val Arg Phe Glu His Ala		
	805	810 815
Val Gln Gly Leu Val Glu Arg Gly Phe Gly Leu Phe Ile Glu Met Ser		
	820	825 830
Ala His Pro Val Leu Thr Thr Ala Val Glu Glu Thr Gly Ala Glu Ser		
	835	840 845
Glu Thr Ala Val Ala Ala Val Gly Thr Leu Arg Arg Asp Ser Gly Gly		
	850	855 860
Leu Arg Arg Leu Leu His Ser Leu Ala Glu Ala Tyr Val Arg Gly Ala		
865	870	875 880
Thr Val Asp Trp Ala Val Ala Phe Gly Gly Ala Gly Arg Arg Leu Asp		
	885	890 895
Leu Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Asp Lys Gly		
	900	905 910
Ala Ala Ser Asp Glu Ala Arg Ala Val Ser Asp Pro Ala Ala Gly Trp		

915

920

925

Phe Trp Gln Ala Val Ala Arg Gln Asp Leu Lys Ser Val Ser Asp Ala
930 935 940

Leu Asp Leu Asp Ala Asp Ala Pro Leu Ser Ala Thr Leu Pro Ala Leu
945 950 955 960

Ser Val Trp His Arg Gln Glu Arg Glu Arg Val Leu Ala Asp Gly Trp
965 970 975

Arg Tyr Arg Val Asp Trp Val Arg Val Ala Pro Gln Pro Val Arg Arg
980 985 990

Thr Arg Glu Thr Trp Leu Leu Val Val Pro Pro Gly Gly Ile Glu Glu
995 1000 1005

Ala Leu Val Glu Arg Leu Thr Asp Ala Leu Asn Thr Arg Gly Ile Ser
1010 1015 1020

Thr Leu Arg Leu Asp Val Pro Pro Ala Ala Thr Ser Gly Glu Leu Ala
1025 1030 1035 1040

Thr Glu Leu Arg Ala Ala Ala Asp Gly Asp Pro Val Lys Ala Ile Leu
1045 1050 1055

Ser Leu Thr Ala Leu Asp Glu Arg Pro His Pro Glu Cys Lys Asp Val
1060 1065 1070

Pro Ser Gly Ile Ala Leu Leu Leu Asn Leu Val Lys Ala Leu Gly Glu
1075 1080 1085

Ala Asp Leu Arg Ile Pro Leu Trp Thr Ile Thr Arg Gly Ala Val Lys
1090 1095 1100

Ala Gly Pro Ala Asp Arg Leu Leu Arg Pro Met Gln Ala Gln Ala Trp
1105 1110 1115 1120

Gly Leu Gly Arg Val Ala Ala Leu Glu His Pro Glu Arg Trp Gly Gly
1125 1130 1135

Leu Ile Asp Leu Pro Asp Ser Leu Asp Gly Asp Val Leu Thr Arg Leu
1140 1145 1150

Gly Glu Ala Leu Thr Asn Gly Leu Ala Glu Asp Gln Leu Ala Ile Arg
1155 1160 1165

Gln Ser Gly Val Leu Ala Arg Arg Leu Val Pro Ala Pro Ala Asn Gln

1170	1175	1180
Pro Ala Gly Arg Lys Trp Arg Pro Arg Gly Ser Ala Leu Ile Thr Gly		
185	1190	1195 1200
Gly Leu Gly Ala Val Gly Ala Gln Val Ala Arg Trp Leu Ala Glu Ile		
1205	1210	1215
Gly Ala Glu Arg Ile Val Leu Thr Ser Arg Arg Gly Asn Gln Ala Ala		
1220	1225	1230
Gly Ala Ala Glu Leu Glu Ala Glu Leu Arg Ala Leu Gly Ala Gln Val		
1235	1240	1245
Ser Ile Val Ala Cys Asp Val Thr Asp Arg Ala Glu Met Ser Ala Leu		
1250	1255	1260
Leu Ala Glu Phe Asp Val Thr Ala Val Phe His Ala Ala Gly Val Gly		
265	1270	1275 1280
Arg Leu Leu Pro Leu Ala Glu Thr Asp Gln Asn Gly Leu Ala Glu Ile		
1285	1290	1295
Cys Ala Ala Lys Val Arg Gly Ala Gln Val Leu Asp Glu Leu Cys Asp		
1300	1305	1310
Ser Thr Asp Leu Asp Ala Phe Val Leu Phe Ser Ser Gly Ala Gly Val		
1315	1320	1325
Trp Gly Gly Gly Gly Gln Gly Ala Tyr Gly Ala Ala Asn Ala Phe Leu		
1330	1335	1340
Asp Thr Leu Ala Glu Gln Arg Arg Ala Arg Gly Leu Pro Ala Thr Ser		
345	1350	1355 1360
Ile Ser Trp Gly Ser Trp Ala Gly Gly Gly Met Ala Asp Gly Ala Ala		
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Gly Glu His Leu Arg Arg Arg Gly Ile Arg Pro Met Pro Ala Ala Ser		
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Ala Ile Leu Ala Leu Gln Glu Val Leu Asp Gln Asp Glu Thr Cys Val		
1395	1400	1405
Ser Ile Ala Asp Val Asp Trp Asp Arg Phe Val Pro Thr Phe Ala Ala		
1410	1415	1420
Thr Arg Ala Thr Arg Leu Phe Asp Glu Val Pro Ala Ala Arg Lys Ala		

425	1430	1435	1440
Met Pro Ala Asn Gly Pro Ala Glu Pro Gly Gly Ser Pro Phe Ala Arg	1445	1450	1455
Asn Leu Ala Glu Leu Pro Glu Ala Gln Arg Arg His Glu Leu Val Asp	1460	1465	1470
Leu Val Cys Ala Gln Val Ala Thr Val Leu Gly His Gly Ser Arg Glu	1475	1480	1485
Glu Val Gln Pro Glu Arg Ala Phe Arg Ala Leu Gly Phe Asp Ser Leu	1490	1495	1500
Met Ala Val Asp Leu Arg Asn Arg Leu Thr Thr Ala Thr Gly Leu Arg	505	1510	1515
Leu Pro Thr Thr Thr Val Phe Asp Tyr Pro Asn Pro Ala Ala Leu Ala	1525	1530	1535
Ala His Leu Leu Glu Glu Leu Val Gly Asp Val Ala Ser Ala Ala Val	1540	1545	1550
Thr Ala Ala Ser Ala Pro Ala Ser Asp Glu Pro Ile Ala Ile Val Ala	1555	1560	1565
Met Ser Cys Arg Phe Pro Gly Gly Ala His Ser Pro Glu Asp Leu Trp	1570	1575	1580
Arg Leu Val Ala Ala Gly Thr Glu Val Ile Gly Glu Phe Pro Ser Asp	585	1590	1595
Arg Gly Trp Asp Ala Glu Gly Leu Tyr Asp Pro Asp Ala Ser Arg Pro	1605	1610	1615
Gly Thr Thr Tyr Ala Arg Met Ala Gly Phe Leu Tyr Asp Ala Gly Glu	1620	1625	1630
Phe Asp Ala Asp Leu Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met	1635	1640	1645
Asp Pro Gln Gln Arg Leu Val Leu Glu Ile Ala Trp Glu Ala Leu Glu	1650	1655	1660
Arg Ala Gly Ile Asp Pro Leu Ser Leu Lys Gly Ser Gly Val Gly Thr	665	1670	1675
Tyr Ile Gly Ala Gly Ser Arg Gly Tyr Ala Thr Asp Val Arg Gln Phe			1680

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Pro Glu Glu Ala Glu Gly Tyr Leu Leu Thr Gly Thr Ser Ala Ser Val		
1700	1705	1710
Leu Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val		
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Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala		
1730	1735	1740
Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly		
745	1750	1755 1760
Val Thr Val Met Ser Thr Pro Glu Met Phe Val Glu Phe Ser Arg Gln		
1765	1770	1775
Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala		
1780	1785	1790
Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg		
1795	1800	1805
Leu Ser Asp Ala His Arg Asn Gly His Arg Val Leu Ala Val Val Arg		
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Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Ala Ala Pro		
825	1830	1835 1840
Asn Gly Pro Ser Gln Gln Arg Val Ile Asn Gln Ala Leu Ala Asn Ala		
1845	1850	1855
Ala Leu Ser Ala Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly		
1860	1865	1870
Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr		
1875	1880	1885
Gly Gln Ala Arg Glu Arg Asp Arg Pro Leu Trp Leu Gly Ser Val Lys		
1890	1895	1900
Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile		
905	1910	1915 1920
Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro Ala Ser Leu His		
1925	1930	1935
Ala Asp Glu Pro Thr Ser Glu Val Asp Trp Ser Ser Gly Ala Val Arg		

1940

1945

50

Leu Leu Ala Glu Gln Val Pro Trp Pro Glu Ser Asp Arg Val Arg Arg
 1955 1960 1965

Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile
 1970 1975 1980

Leu Glu Gln Ala Thr Asn Ala Pro Asp Ser Thr Ala Glu Thr Asp Lys
 985 1990 1995 2000

Thr Glu Ser Gly Ser Thr Val Asp Ile Pro Val Val Pro Trp Leu Val
 2005 2010 2015

Ser Gly Lys Thr Thr Asp Ser Leu Arg Gly Gln Ala Glu Arg Val Leu
 2020 2025 2030

Ser Gln Val Glu Ser Arg Pro Glu Gln Arg Ser Leu Asp Val Ala Tyr
 2035 2040 2045

Ser Leu Ala Ser Gly Arg Ala Ala Leu Asp Glu Arg Ala Val Val Leu
 2050 2055 2060

Gly Ala Asp Arg Gly Glu Leu Val Ala Gly Leu Ala Ala Leu Ala Ala
 065 2070 2075 2080

Gly Gln Glu Ala Ser Gly Val Ile Ser Gly Thr Arg Ala Ser Ala Arg
 2085 2090 2095

Phe Gly Phe Val Phe Ser Gly Gln Gly Gly Gln Trp Leu Gly Met Gly
 2100 2105 2110

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Ala Cys Ala Glu Leu Glu Ala His Leu Gly Glu Asp Arg Arg Val Arg
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Gly Ser Trp Gly Val Arg Pro Asp Val Val Met Gly His Ser Val Gly
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Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Leu Ser Leu Arg Asp Ala

2195

2200

2205

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Asp Gly Ala Met Leu Ala Val Ala Ala Gly Glu Asp Leu Val Arg Pro
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Leu Leu Ala Gly Arg Glu Glu Ser Val Ser Val Ala Ala Leu Asn Ala
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Pro Gly Ser Val Val Leu Ser Gly Asp Arg Glu Val Leu Ala Ser Ile
2260 2265 2270

Val Gly Arg Leu Thr Glu Leu Arg Val Arg Thr Arg Arg Leu Arg Val
2275 2280 2285

Ser His Ala Phe His Ser His Arg Met Asp Pro Met Leu Gly Glu Phe
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Ala Gln Ile Ala Glu Ser Ala Glu Phe Gly Lys Pro Thr Thr Pro Leu
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Val Ser Thr Leu Thr Gly Glu Leu Asp Arg Ala Ala Glu Met Ser Thr
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Pro Gly Tyr Trp Val Arg Gln Ala Arg Glu Pro Val Arg Phe Ala Asp
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Gly Val Gln Ala Leu Ala Ala Gln Gly Ile Gly Thr Val Val Glu Leu
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Gly Pro Asp Gly Thr Leu Ala Ala Leu Val Arg Glu Cys Ala Thr Glu
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2435 2440 2445

Ile Glu Ser Ser Ala Arg Pro Ala Arg Asp Arg Ala Asp Ile Gly Glu

2450

2455

2460

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Val Pro Gly Ala Ala Asp Asp Gly Leu Val Thr Ala Leu Thr Ser Ser
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Trp Ala Val Thr Arg Gly Gly Val Ala Leu Glu Asp Val Arg Val Ser
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Pro Glu Gln Ala Leu Val Trp Gly Leu Leu Arg Val Ala Gly Leu Glu
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His Pro Glu Phe Trp Gly Gly Leu Ile Asp Leu Pro Ser Asp Trp Asp
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Asp Arg Leu Gly Ala Arg Leu Ala Gly Val Leu Ala Asp Gly Gly Glu
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Asp Gln Val Ala Ile Arg Arg Gly Gly Val Phe Val Arg Arg Leu Glu

705

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Val Met Phe Ser Ser Val Ser Gly Val Trp Gly Ala Gly Gly Gln Gly
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29

2970

2975

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Glu Leu Phe Pro Thr Glu Thr Thr Val Asp Ser Ala Leu Ala Glu Leu
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Asp Leu His Gln Thr Arg Gln Arg Leu Leu Ala Ala Glu Ser Arg Ser	
20 25 30	
cag gag ccg atc gcg atc gtc tcg gcg agc tgc cga ctg ccc ggc ggc	144
Gln Glu Pro Ile Ala Ile Val Ser Ala Ser Cys Arg Leu Pro Gly Gly	
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gtc gac tct ccc gaa gcg ctc tgg caa ctc gtg cgc act ggc acc gac	192
Val Asp Ser Pro Glu Ala Leu Trp Gln Leu Val Arg Thr Gly Thr Asp	
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Ala Ile Ser Glu Phe Pro Ala Asp Arg Gly Trp Asp Leu Gly Arg Leu	
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Tyr Asp Pro Asp Pro Asn His Gln Gly Thr Ser Tyr Thr Arg Ala Gly	
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Gly Phe Leu Ala Gly Ala Gly Asp Phe Asp Pro Ala Met Phe Gly Ile	
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Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu	
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Glu Leu Ser Trp Glu Ala Leu Glu Arg Ala Gly Ile Asp Pro Thr Ser	
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Leu Arg Gly Ser Lys Thr Gly Val Phe Gly Gly Val Thr Pro Gln Glu	
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Tyr Gly Pro Ser Leu Gln Glu Met Ser Arg Asn Ala Gly Gly Phe Gly	

165

170

175

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 Leu Thr Gly Arg Met Val Ser Val Ala Ser Gly Arg Val Ala Tyr Ser
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 Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser
 195 200 205

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 Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Ser Gly Glu
 210 215 220

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 Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ala Thr Pro Ala
 225 230 235 240

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 Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg
 245 250 255

tgc aag tcg ttc gcg gct gcc gcg gat ggc acc ggg tgg ggt gag ggt 816
 Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
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 Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly
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 His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly
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 Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val
 305 310 315 320

atc acc cag gcg ttg gcg agt gcg ggg ctg tcg gtt tcc gat gtg gat 1008
 Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val Ser Asp Val Asp
 325 330 335

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355

360

365

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Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Leu Ala Met Arg His	
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Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu Pro Thr Ser Ala Val	
405 410 415	
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Asp Trp Ser Ala Gly Ser Val Arg Leu Leu Thr Glu Asn Thr Pro Trp	
420 425 430	
ccg gac agt ggt cgt cct tgc cgg gtg ggg gtg tcg tcg ttc ggg atc	1344
Pro Asp Ser Gly Arg Pro Cys Arg Val Gly Val Ser Ser Phe Gly Ile	
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Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Ser Pro Val Glu Gln	
450 455 460	
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Gly Glu Pro Ala Gly Pro Val Glu Gly Glu Arg Glu Pro Asp Val Ala	
465 470 475 480	
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Val Pro Val Val Pro Trp Val Leu Ser Gly Lys Thr Pro Glu Ala Ala	
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Arg Ala Gln Ala Glu Arg Val His Ser His Ile Glu Asp Arg Pro Gly	
500 505 510	
ctg tcg ccg gtg gat gtg gcg tat tcg cta gga atg aca cgc gcg gcg	1584
Leu Ser Pro Val Asp Val Ala Tyr Ser Leu Gly Met Thr Arg Ala Ala	
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Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Ala Ala Leu Leu	
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Thr Gly Leu Arg Ala Phe Ala Asp Gly Cys Asp Ala Pro Glu Val Val	

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Ser Gly Ser Val Gly Leu Gly Gly Arg Val Gly Phe Val Phe Ser Gly				
565	570	575		
cag ggt ggt cag tgg ccg ggg atg ggc cgg ggg ctc tac tcg gtg ttt	1776			
Gln Gly Gly Gln Trp Pro Gly Met Gly Arg Gly Leu Tyr Ser Val Phe				
580	585	590		
ccg gtg ttc gcc gac gcg ttc gac gag gct tgc gcg gag ttg gat gca	1824			
Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp Ala				
595	600	605		
cac ctg ggc cag gaa ctg cgg gtt cgg gat gtg gtg ttc ggt tcg caa	1872			
His Leu Gly Gln Glu Leu Arg Val Arg Asp Val Val Phe Gly Ser Gln				
610	615	620		
gcg tgg ttg ctg gat cgg acg gtg tgg gcg cag tcg ggt ttg ttc gcg	1920			
Ala Trp Leu Leu Asp Arg Thr Val Trp Ala Gln Ser Gly Leu Phe Ala				
625	630	635	640	
ttg cag att ggc ttg ctg cgg ctg ctg ggt tcg tgg ggt gtt cgg ccg	1968			
Leu Gln Ile Gly Leu Leu Arg Leu Leu Gly Ser Trp Gly Val Arg Pro				
645	650	655		
gat gtg gtg ttg ggg cac tcg gtg ggt gag ctg gct gcg gtg cat gcg	2016			
Asp Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Val His Ala				
660	665	670		
gct ggt gtg ttg tcg ttg tcg gag gcc gcg cgg ttg gtg gcg ggt cgc	2064			
Ala Gly Val Leu Ser Leu Ser Glu Ala Ala Arg Leu Val Ala Gly Arg				
675	680	685		
gcc cgg ttg atg cag gcg ttg cct tct ggt ggt gcc atg ctc gcg gtc	2112			
Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala Met Leu Ala Val				
690	695	700		
gct acg ggt gag ttt cag gtc gat cct ctg ctg gat ggg gtg cgg gac	2160			
Ala Thr Gly Glu Phe Gln Val Asp Pro Leu Leu Asp Gly Val Arg Asp				
705	710	715	720	
cgg atc ggt atc gcg gcg gtg aat ggc ccg gaa tcg gtt gtg ctc tct	2208			
Arg Ile Gly Ile Ala Ala Val Asn Gly Pro Glu Ser Val Val Leu Ser				
725	730	735		
ggt gac cgc gag ctg ctc acc gag atc gct gat cgg ttg cac gat cag	2256			
Gly Asp Arg Glu Leu Leu Thr Glu Ile Ala Asp Arg Leu His Asp Gln				

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Gly Cys Arg Thr Arg Trp Leu Arg Val Ser His Ala Phe His Ser Pro			
755	760	765	
cat atg gag ccg atg ctg gag gag ttc gcc cag atc tcc cga ggc cgc			2352
His Met Glu Pro Met Leu Glu Glu Phe Ala Gln Ile Ser Arg Gly Arg			
770	775	780	
gaa tat cac gca ccg gaa ctg ccg atc atc tgc acc ctg atc ggt gag			2400
Glu Tyr His Ala Pro Glu Leu Pro Ile Ile Ser Thr Leu Ile Gly Glu			
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Leu Asp Gly Gly Arg Val Met Gly Thr Pro Glu Tyr Trp Val Arg Gln			
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gtg cgt gag ccc gtc cgt ttc gcc gag ggt gtc cag gcg ctt gtc ggt			2496
Val Arg Glu Pro Val Arg Phe Ala Glu Gly Val Gln Ala Leu Val Gly			
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cag ggt gtc ggc acg att gtc gaa ttg ggt ccg gac ggg gcg ttg tgc			2544
Gln Gly Val Gly Thr Ile Val Glu Leu Gly Pro Asp Gly Ala Leu Ser			
	835	840	845
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Thr Leu Val Glu Glu Cys Val Ala Glu Ser Gly Arg Val Ala Gly Ile			
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Pro Leu Met Arg Lys Asp Arg Asp Glu Ala Arg Thr Val Leu Ala Ala			
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Leu Ala Gln Ile His Thr Arg Gly Gly Glu Val Asp Trp Arg Ser Phe			
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Phe Ala Gly Thr Gly Ala Lys Gln Val Asp Leu Pro Thr Tyr Ala Phe			
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cag cgg cag cgg tac tgg ctg gca tcc acc ggg cgt gcg ggt gac gtg			2784
Gln Arg Gln Arg Tyr Trp Leu Ala Ser Thr Gly Arg Ala Gly Asp Val			
	915	920	925
acc gcc gcc gga ttg gcc gag gcg gac cat ccg ctg ctc ggt gcg gtg			2832
Thr Ala Ala Gly Leu Ala Glu Ala Asp His Pro Leu Leu Gly Ala Val			

930

935

940

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 Val Val Pro Gly Thr Ala Ile Val Glu Leu Val Trp His Val Gly Glu
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 Arg Leu Gly Cys Gly Arg Val Glu Glu Leu Ala Leu Glu Ala Pro Leu
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 Ile Leu Pro Asp His Gly Ala Val Gln Val Gln Val Leu Val Gly Pro
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Thr Thr Ala Gly Asp Asp Leu Ala Ile Val Gly Asp Gly Pro Ser Trp			
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Pro Glu Ser Val Arg Ala Thr Ala Arg Phe Ala Thr Leu Asp Glu Phe			
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Arg Ala Ala Val Asp Ser Asp Val Pro Ala Pro Gly Ser Val Leu Val			
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Ala Ala Met Ser Ala Glu Glu Val Glu Gly Gly Ser Leu Pro Ser Arg			
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Pro Ala Ala Val Arg Ala Gly Glu Pro Gln Leu Ala Leu Arg Arg Gly			
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Val Ala Leu Val Pro Arg Leu Ala Arg Leu Thr Val Arg Glu Glu Gly			
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Thr Gly Ala Leu Gly Gly Val Val Ala Arg His Leu Val Glu Glu His			
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Gly Val His Glu Leu Val Asp Glu Leu Ala Arg Ala Gly Ala Val Val			
1460	1465	1470	
gag gtg gtg gct tgc gat gtg gct gac cgc acc gat ctg gag cac gtg	4464		
Glu Val Val Ala Cys Asp Val Ala Asp Arg Thr Asp Leu Glu His Val			
1475	1480	1485	
ctg gcc gcc att ccg gtc gac tgg ccg ctg cgg ggg atc gtg cat acc	4512		
Leu Ala Ala Ile Pro Val Asp Trp Pro Leu Arg Gly Ile Val His Thr			
1490	1495	1500	
gct ggg gtg ctg gcc gac gga gtg atc ggg tcc ttg tcg gcg gcg gat	4560		
Ala Gly Val Leu Ala Asp Gly Val Ile Gly Ser Leu Ser Ala Ala Asp			

1505	1510	1515	1520	
gtg ggc acg gtg ttt gcc ccg aag gtg acg ggg gca tgg cat ctg cac				4608
Val Gly Thr Val Phe Ala Pro Lys Val Thr Gly Ala Trp His Leu His				
1525		1530	1535	
gag ttg acc cgc gat ctg gat ctg tgg ttc ttc gtt ctt ttc tct tcc				4656
Glu Leu Thr Arg Asp Leu Asp Leu Ser Phe Phe Val Leu Phe Ser Ser				
1540	1545		1550	
ttc tcc ggg att gcg ggt gcc gca ggg cag gcc aac tac gcg gcg gcg				4704
Phe Ser Gly Ile Ala Gly Ala Ala Gly Gln Ala Asn Tyr Ala Ala Ala				
1555	1560		1565	
aac acg ttc ctg gat gca ttg gcg cgt tat cgc cgg gcg cgt ggg ctg				4752
Asn Thr Phe Leu Asp Ala Leu Ala Arg Tyr Arg Arg Ala Arg Gly Leu				
1570	1575		1580	
cct ggg ttg tgg ttg gcg tgg gga ctg tgg gcg caa ccc agc ggt atg				4800
Pro Gly Leu Ser Leu Ala Trp Gly Leu Trp Ala Gln Pro Ser Gly Met				
1585	1590	1595	1600	
acg agt ggc ttg gac gcg gcg tgg gtg gag cgg ttg gcg cgg acg ggc				4848
Thr Ser Gly Leu Asp Ala Ala Ser Val Glu Arg Leu Ala Arg Thr Gly				
1605	1610		1615	
atc gca gaa ctt tcc acg gag gat gga ctc cgc ctg ttc gat gcc gcg				4896
Ile Ala Glu Leu Ser Thr Glu Asp Gly Leu Arg Leu Phe Asp Ala Ala				
1620	1625		1630	
ttc gcg aag gac cgg gct tgc gtc gtt gcc gct cga ttg gac agg gcg				4944
Phe Ala Lys Asp Arg Ala Cys Val Val Ala Ala Arg Leu Asp Arg Ala				
1635	1640		1645	
ctg ctg gtc ggg aac gga cga tgg cac gcg att ccg gcg ctg ttg agc				4992
Leu Leu Val Gly Asn Gly Arg Ser His Ala Ile Pro Ala Leu Leu Ser				
1650	1655		1660	
gcg ttg gtt cct gtt cgc ggc ggt gtg gcg agg aaa aca gcc aat tct				5040
Ala Leu Val Pro Val Arg Gly Gly Val Ala Arg Lys Thr Ala Asn Ser				
1665	1670	1675	1680	
cag gcc gcg gat gag gac gca ctg ttg ggt ttg gtg cgg gag cac gtt				5088
Gln Ala Ala Asp Glu Asp Ala Leu Leu Gly Leu Val Arg Glu His Val				
1685	1690		1695	
tgg gcc gtg ctg ggt tat tgg ggt gcg gtc gag gtt ggg ggc gac cgt				5136
Ser Ala Val Leu Gly Tyr Ser Gly Ala Val Glu Val Gly Gly Asp Arg				

1700

1705

1710

gct ttc cgt gat ctg ggt ttt gat tcg ttg tct ggc gtg gag ttg cgg 5184
 Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg
 1715 1720 1725

aac cgc ctt gcc ggg gtg ctg ggg gtg cgg ttg ccg gcg act gcg gtg 5232
 Asn Arg Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val
 1730 1735 1740

ttc gac tat ccg acg ccg cgg gcg ctg gcg cgt ttc ctg cat cag gaa 5280
 Phe Asp Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu
 1745 1750 1755 1760

ctg gca ggc gag gtc gcg tcc acg tcg acg ccg gtg acc agg gca gcg 5328
 Leu Ala Gly Glu Val Ala Ser Thr Ser Thr Pro Val Thr Arg Ala Ala
 1765 1770 1775

agt gcc gaa gag gat ctt gtt gcg att gtc ggg atg gga tgt cgt ttt 5376
 Ser Ala Glu Glu Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe
 1780 1785 1790

ccg ggt ggg gtg tcg tcg ccg gag gag ctt tgg cgg ctg gtg gcc ggc 5424
 Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly
 1795 1800 1805

ggc gtg gat gcg gtg gct ggg ttc cca gac gat cgc ggc tgg gat ctc 5472
 Gly Val Asp Ala Val Ala Gly Phe Pro Asp Asp Arg Gly Trp Asp Leu
 1810 1815 1820

gcg gcg ttg tac gat cct gat ccc gat cgt ctc ggg acc tcg tat gtg 5520
 Ala Ala Leu Tyr Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr Val
 1825 1830 1835 1840

tgt gag ggc ggg ttt ctg cgg gac gcg gcg gag ttc gat gct gac atg 5568
 Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Asp Met
 1845 1850 1855

ttc ggc atc agc ccg cgt gag gcg ttg gcg atg gat ccg cag cag cgg 5616
 Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
 1860 1865 1870

ttg ctg ctg gag gtc gcc tgg gaa acc ttg gag cgg gct ggg atc gat 5664
 Leu Leu Leu Glu Val Ala Trp Glu Thr Leu Glu Arg Ala Gly Ile Asp
 1875 1880 1885

ccg ttc tcg ttg cac ggc agc cgg acc ggt gtg ttc gcg ggc ttg atg 5712
 Pro Phe Ser Leu His Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met

1890	1895	1900	
tac cac gac tat ggg gcc cga ttc att acc aga gca ccg gag ggc ttc			5760
Tyr His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly Phe			
1905	1910	1915	1920
gaa ggg cac ctc ggg acg ggc aat gcg ggg agc gtg ctg tcg ggt cgg			5808
Glu Gly His Leu Gly Thr Gly Asn Ala Gly Ser Val Leu Ser Gly Arg			
1925	1930	1935	
gtt gcg tat tcg ttt ggt ttc gag ggt cct gcg gtg acg gtg gat acg			5856
Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr			
1940	1945	1950	
gcg tgt tcg tcg tcg ttg gtg gcg tta cac ctg gcg ggt caa gca ctg			5904
Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu			
1955	1960	1965	
cgg gcc ggt gag tgc gaa ttc gcc ctt gcc ggt ggc gtc acg gtg atg			5952
Arg Ala Gly Glu Cys Glu Phe Ala Leu Ala Gly Gly Val Thr Val Met			
1970	1975	1980	
tcg acg ccg acg acg ttc gtg gag ttc tcc cgt caa ccg ggt ctg gct			6000
Ser Thr Pro Thr Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala			
1985	1990	1995	2000
ccg gat ggg ccg tgc aag tcg ttc gcg gcg gcc gcg gat ggc acc ggg			6048
Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly			
2005	2010	2015	
tgg ggc gag ggt gcc ggt ctg gtg ttg ctg gag ccg ttg tcg gat gcc			6096
Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala			
2020	2025	2030	
cgg cgc aat ggg cac gag gtt ctg gcg gtg gtg ccg ggt agc gcg gtg			6144
Arg Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val			
2035	2040	2045	
aac cag gac ggc gcg tcg aat ggc ttg act gcg cca aat ggt ccg tca			6192
Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser			
2050	2055	2060	
cag caa agg gtg atc acc cag gca ctc acg agt gcc ggg ctg tcc gtg			6240
Gln Gln Arg Val Ile Thr Gln Ala Leu Thr Ser Ala Gly Leu Ser Val			
2065	2070	2075	2080
tcc gac gtg gat gct gtg gag gcg cat ggg acg ggc acg ccg ctt ggt			6288
Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly			

gat ccg atc gag gcg cag gcg ttg atc gct acg tac ggc cgg gat cgt Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg 2100 2105 2110	6336
gat ccc ggt cgg ccg ttg tgg ctg ggg tcg gtg aag tcg aat att ggt Asp Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly 2115 2120 2125	6384
cac acc cag gcg gcg gcg ggt gtc gct ggt gtg atc aag atg gtg atg His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met 2130 2135 2140	6432
gcg atg cgg cag ggg gag ctg ccg cgc acg ttg cac gtg gac gag ccc Ala Met Arg Gln Gly Glu Leu Pro Arg Thr Leu His Val Asp Glu Pro 2145 2150 2155 2160	6480
tcc gcg cag gtg gac tgg tct gcg ggc acg gtc caa ctc ctc acg gag Ser Ala Gln Val Asp Trp Ser Ala Gly Thr Val Gln Leu Leu Thr Glu 2165 2170 2175	6528
aac acg ccc tgg ccc gac agc ggt cgt ctt cgc cgg gcg ggc gtg tca Asn Thr Pro Trp Pro Asp Ser Gly Arg Leu Arg Arg Ala Gly Val Ser 2180 2185 2190	6576
tcg ttc ggg atc agt ggc acc aac gcg cac ctg atc ctt gaa caa cct Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile Leu Glu Gln Pro 2195 2200 2205	6624
ccg cga gag tcg cag cgc tca aca gag ccg gat tcg ggt tct gtc cgc Pro Arg Glu Ser Gln Arg Ser Thr Glu Pro Asp Ser Gly Ser Val Arg 2210 2215 2220	6672
gat ttt ccg gtg gtg ccg tgg atg gtg tcg ggc aaa aca ccc gaa gcg Asp Phe Pro Val Val Pro Trp Met Val Ser Gly Lys Thr Pro Glu Ala 2225 2230 2235 2240	6720
cta tcc gcc cag gca gat gca ttg atg tcc tac ttg agc aat cgc gtt Leu Ser Ala Gln Ala Asp Ala Leu Met Ser Tyr Leu Ser Asn Arg Val 2245 2250 2255	6768
gat gct tcc ccg cga gat atc ggt tat tcg ctt gcg gtg acc cgt ccg Asp Ala Ser Pro Arg Asp Ile Gly Tyr Ser Leu Ala Val Thr Arg Pro 2260 2265 2270	6816
gcg ttg gac cac cgc gct gtc gtg ctg ggt gcg gat cgt gcc gcg ttg Ala Leu Asp His Arg Ala Val Val Leu Gly Ala Asp Arg Ala Ala Leu	6864

2275	2280	2285	
ctg ccg ggc ttg aaa gcg ctg gcc gtt agt aat gac gct gcc gag gtg			6912
Leu Pro Gly Leu Lys Ala Leu Ala Val Ser Asn Asp Ala Ala Glu Val			
2290	2295	2300	
atc acc ggc act cgt gcc gct ggg ccg gtc gga ttc gtg ttc tcc ggt			6960
Ile Thr Gly Thr Arg Ala Ala Gly Pro Val Gly Phe Val Phe Ser Gly			
2305	2310	2315	2320
caa ggt ggt cag tgg ccc ggg atg gga agc ggg ctg cac tgc gcg ttt			7008
Gln Gly Gly Gln Trp Pro Gly Met Gly Ser Gly Leu His Ser Ala Phe			
2325	2330	2335	
ccg gtg ttc gcc gac gcg ttt gac gaa gcc tgc tgc gag ctg gat gcg			7056
Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Cys Glu Leu Asp Ala			
2340	2345	2350	
cat ctg ggg cag atg gcc cgg cta cga gat gtg ttg tcc ggt tgc gat			7104
His Leu Gly Gln Met Ala Arg Leu Arg Asp Val Leu Ser Gly Ser Asp			
2355	2360	2365	
acg caa ctt ctg gac cag acc ttg tgg gcg cag ccg ggc ctg ttc gcg			7152
Thr Gln Leu Leu Asp Gln Thr Leu Trp Ala Gln Pro Gly Leu Phe Ala			
2370	2375	2380	
ttg caa gtc gga ctg tgg gag ttg ttg ggt tgc tgg ggt gtc cgg ccc			7200
Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Ser Trp Gly Val Arg Pro			
2385	2390	2395	2400
gct gtg gtg ctg ggc cac tgc gtc ggt gag ctg gcg gcg gcg ttc gcg			7248
Ala Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe Ala			
2405	2410	2415	
gct gga gtg ttg tgc ttg cgg gat gcg gct cgg ctg gtg gcg ggc cgt			7296
Ala Gly Val Leu Ser Leu Arg Asp Ala Ala Arg Leu Val Ala Gly Arg			
2420	2425	2430	
gcc cgg ttg atg caa gcc ctg cca act ggc ggt gcc atg ctg gct gcg			7344
Ala Arg Leu Met Gln Ala Leu Pro Thr Gly Gly Ala Met Leu Ala Ala			
2435	2440	2445	
gct gct gga gag gag cag ctg cgc ccg ttg ctg gcc gac tgc ggt gat			7392
Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala Asp Cys Gly Asp			
2450	2455	2460	
cgt gtg ggg atc gcc gcg gtc aac gct ccc ggg tgc gtg gtg ctg tcc			7440
Arg Val Gly Ile Ala Ala Val Asn Ala Pro Gly Ser Val Val Leu Ser			

2465	2470	2475	2480	
ggt gat cgg gat gtg ctc gat gac att gcc ggt cgg ctg gac ggg caa				7488
Gly Asp Arg Asp Val Leu Asp Asp Ile Ala Gly Arg Leu Asp Gly Gln				
2485	2490	2495		
ggg atc cgg tcc agg tgg ttg cgg gtt tcg cat gcg ttt cat tcg cat				7536
Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser His				
2500	2505	2510		
cgg atg gat ccg atg ctg gcg gag ttc acc gaa atc gcc cgg agc gtg				7584
Arg Met Asp Pro Met Leu Ala Glu Phe Thr Glu Ile Ala Arg Ser Val				
2515	2520	2525		
gac tac cgg tcg tca ggg ctg ccg atc gtg tcg acg ttg acg ggt gag				7632
Asp Tyr Arg Ser Ser Gly Leu Pro Ile Val Ser Thr Leu Thr Gly Glu				
2530	2535	2540		
ctc gat gag gtc ggc atg ccg gct acg ccg gag tat tgg gtg cgc cag				7680
Leu Asp Glu Val Gly Met Pro Ala Thr Pro Glu Tyr Trp Val Arg Gln				
2545	2550	2555	2560	
gtg cga gaa ccc gtc cgc ttc gcc gac ggt gtt gct gcg ctc gcg gct				7728
Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Ala Ala Leu Ala Ala				
2565	2570	2575		
cac ggt gtg agc acc gtc gtc gag gtc ggt ccg gat ggg gtg ttg tcg				7776
His Gly Val Ser Thr Val Val Glu Val Gly Pro Asp Gly Val Leu Ser				
2580	2585	2590		
gcg ctg gtg cag gag tgc gcg gcc gga tcc gat cag gcc gga cgg gtg				7824
Ala Leu Val Gln Glu Cys Ala Ala Gly Ser Asp Gln Gly Gly Arg Val				
2595	2600	2605		
gcc gcg gtt ccg ctc atg cgc agc aat cgc gac gag gcg cac acg gtg				7872
Ala Ala Val Pro Leu Met Arg Ser Asn Arg Asp Glu Ala His Thr Val				
2610	2615	2620		
aca acg gca ttg gcg cag atc cat gtg cgt ggt gct gag gtg gac tgg				7920
Thr Thr Ala Leu Ala Gln Ile His Val Arg Gly Ala Glu Val Asp Trp				
2625	2630	2635	2640	
cgg tcg ttt ttc gcc ggt acc ggg gca aag cag gtc gag ctg ccc acg				7968
Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Val Glu Leu Pro Thr				
2645	2650	2655		
tat gcc ttc caa cga cag cgg tac tgg ctt gac tca cca tcc gaa ccg				8016
Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Asp Ser Pro Ser Glu Pro				

2660	2665	2670	
gtc ggg caa tcc gcc gat ccc gcg cgc cag tcg ggc ttc tgg gaa ctc			8064
Val Gly Gln Ser Ala Asp Pro Ala Arg Gln Ser Gly Phe Trp Glu Leu			
2675	2680	2685	
gtc gag cag gaa gat gtc agc gcg ctc agc gcc gct ctg cac att acc			8112
Val Glu Gln Glu Asp Val Ser Ala Leu Ser Ala Ala Leu His Ile Thr			
2690	2695	2700	
ggc gat cac gac gtg cag gcg tcc ctg gaa tcg gtg gtt ccg gtc ctc			8160
Gly Asp His Asp Val Gln Ala Ser Leu Glu Ser Val Val Pro Val Leu			
2705	2710	2715	2720
tcc tcc tgg cat cgc cgg atc cgc aac gaa tcc ctg gtg cac cag tgg			8208
Ser Ser Trp His Arg Arg Ile Arg Asn Glu Ser Leu Val His Gln Trp			
2725	2730	2735	
cgg tac cgg att tcc tgg cat gag cgg gca gat ttg cca gac ccc tcg			8256
Arg Tyr Arg Ile Ser Trp His Glu Arg Ala Asp Leu Pro Asp Pro Ser			
2740	2745	2750	
ttg tcg ggg aca tgg ctc gtc gtc gtg ccg gag ggg tgg tcg gcg agt			8304
Leu Ser Gly Thr Trp Leu Val Val Val Pro Glu Gly Trp Ser Ala Ser			
2755	2760	2765	
cgg caa gtt ctg cgt ttc aac gag atg ttc gag gaa cgg ggt tgc ccg			8352
Arg Gln Val Leu Arg Phe Asn Glu Met Phe Glu Glu Arg Gly Cys Pro			
2770	2775	2780	
gca gtt ctg ttc gag ctc gcc ggg cac gac gag gaa gcc ctg gcg caa			8400
Ala Val Leu Phe Glu Leu Ala Gly His Asp Glu Glu Ala Leu Ala Gln			
2785	2790	2795	2800
cga ttc cgc tcg ttg cct gtt gcg tca ggg gga ata agc ggc gtg ttg			8448
Arg Phe Arg Ser Leu Pro Val Ala Ser Gly Gly Ile Ser Gly Val Leu			
2805	2810	2815	
tcc ttg ctg gcg ctg gat gaa tcg ccg tcc tcg ccg aac gct gct ttg			8496
Ser Leu Leu Ala Leu Asp Glu Ser Pro Ser Ser Pro Asn Ala Ala Leu			
2820	2825	2830	
ccg aat ggc gcg ctg aac tcg ttg gta ctg ctg cga gct ctg cgg gcc			8544
Pro Asn Gly Ala Leu Asn Ser Leu Val Leu Leu Arg Ala Leu Arg Ala			
2835	2840	2845	
gcg gat gtg tcg gcg cca ttg tgg ttg gcg acg tgt ggt ggt gtc gcg			8592
Ala Asp Val Ser Ala Pro Leu Trp Leu Ala Thr Cys Gly Gly Val Ala			

2850	2855	2860	
gtc ggg gat gtg ccg gtg aac ccg ggg cag gcg ctg gtg tgg gga ctg			8640
Val Gly Asp Val Pro Val Asn Pro Gly Gln Ala Leu Val Trp Gly Leu			
2865	2870	2875	2880
ggt cgc gtc gtc ggt ctg gag cat ccg gcc tgg tgg ggt ggc ctg gtc			8688
Gly Arg Val Val Gly Leu Glu His Pro Ala Trp Trp Gly Gly Leu Val			
2885	2890	2895	
gac gtg ccg tgc ttg ctc gat gag gac gct cga gaa cgc ttg tcg gtc			8736
Asp Val Pro Cys Leu Leu Asp Glu Asp Ala Arg Glu Arg Leu Ser Val			
2900	2905	2910	
gtg ttg gca ggt ctt ggc gag gac gag atc gcg gta cgt ccc ggt ggt			8784
Val Leu Ala Gly Leu Gly Glu Asp Glu Ile Ala Val Arg Pro Gly Gly			
2915	2920	2925	
gtg ttc gtg cgg cgg ttg gaa cgc gct ggt gcg gcg tcg ggt gcc ggg			8832
Val Phe Val Arg Arg Leu Glu Arg Ala Gly Ala Ala Ser Gly Ala Gly			
2930	2935	2940	
tcg gtg tgg cgt cct cgg ggg acg gtg ttg gtg acg ggt ggt acg ggc			8880
Ser Val Trp Arg Pro Arg Gly Thr Val Leu Val Thr Gly Gly Thr Gly			
2945	2950	2955	2960
ggt ttg ggg gcg cat gtt gcc cgg tgg ttg gcg ggt gcc ggg gct gag			8928
Gly Leu Gly Ala His Val Ala Arg Trp Leu Ala Gly Ala Gly Ala Glu			
2965	2970	2975	
cat gtg gtg ttg acc agc cgt cga ggc gcg gcg gct ccg ggc gct gga			8976
His Val Val Leu Thr Ser Arg Arg Gly Ala Ala Ala Pro Gly Ala Gly			
2980	2985	2990	
gat ttg cgg gcg gag ctg gag gcg ctg ggc gct cgg gtt tcg atc acg			9024
Asp Leu Arg Ala Glu Leu Glu Ala Leu Gly Ala Arg Val Ser Ile Thr			
2995	3000	3005	
gcc tgc gac gtg gcc gat cgt gac gct ttg gcc gaa gtg ttg gcg acc			9072
Ala Cys Asp Val Ala Asp Arg Asp Ala Leu Ala Glu Val Leu Ala Thr			
3010	3015	3020	
att ccg gat gat tgc ccg ctg acc gcg gtg atg cat gcg gcg ggg gtc			9120
Ile Pro Asp Asp Cys Pro Leu Thr Ala Val Met His Ala Ala Gly Val			
3025	3030	3035	3040
ggt gaa gtc ggc gac gtg gcg tcg atg tgt ttg acc gac ttc gtt ggg			9168
Val Glu Val Gly Asp Val Ala Ser Met Cys Leu Thr Asp Phe Val Gly			

3045	3050	3055	
gtg ctg tcg gcg aag gca ggt ggt gcg gcg aat ctc gat gag ttg ctc			9216
Val Leu Ser Ala Lys Ala Gly Gly Ala Ala Asn Leu Asp Glu Leu Leu			
3060	3065	3070	
gcc gat gtc gag ctg gat gcc ttc gtg ctg ttc tca tcc gtc tcg ggt			9264
Ala Asp Val Glu Leu Asp Ala Phe Val Leu Phe Ser Ser Val Ser Gly			
3075	3080	3085	
gtg tgg ggt gct ggc ggg cag ggc gct tat gcg gcg gcg aat gcc tac			9312
Val Trp Gly Ala Gly Gly Gln Gly Ala Tyr Ala Ala Ala Asn Ala Tyr			
3090	3095	3100	
ttg gat gcg ttg gcg cag cag cgt cgg gca agg ggg ttg gtg ggg act			9360
Leu Asp Ala Leu Ala Gln Gln Arg Arg Ala Arg Gly Leu Val Gly Thr			
3105	3110	3115	3120
gcg gtt gcg tgg ggc ccg tgg gcc ggt gac gga atg gcc gca ggt gaa			9408
Ala Val Ala Trp Gly Pro Trp Ala Gly Asp Gly Met Ala Ala Gly Glu			
3125	3130	3135	
ggc ggt gca cag ctg cgc cgg gcc ggc ctg gtg cca atg gct gcg gat			9456
Gly Gly Ala Gln Leu Arg Arg Ala Gly Leu Val Pro Met Ala Ala Asp			
3140	3145	3150	
cgg gcg ttg ctg gca ctt cag ggc gca ttg gat cgt gac gag aca tcc			9504
Arg Ala Leu Leu Ala Leu Gln Gly Ala Leu Asp Arg Asp Glu Thr Ser			
3155	3160	3165	
ctg gtc gtg gcc gat atg gcg tgg gag agg ttc gcc ccg gtg ttc gcc			9552
Leu Val Val Ala Asp Met Ala Trp Glu Arg Phe Ala Pro Val Phe Ala			
3170	3175	3180	
atg tcc cgt cgg cgt ccg ctg ctc gac gag ctg ccc gaa gca cag cag			9600
Met Ser Arg Arg Arg Pro Leu Leu Asp Glu Leu Pro Glu Ala Gln Gln			
3185	3190	3195	3200
gcg ttg gcg gat gcg gag aac acc act gat gct gcg gac tcg gcc gtc			9648
Ala Leu Ala Asp Ala Glu Asn Thr Thr Asp Ala Ala Asp Ser Ala Val			
3205	3210	3215	
ccg cta ccg cgg ctc gcg ggc atg gca gcc gcc gaa cgc cgc cgc gcg			9696
Pro Leu Pro Arg Leu Ala Gly Met Ala Ala Ala Glu Arg Arg Arg Ala			
3220	3225	3230	
atg ctg gac ctg gtg ctg gcg gag gcc tcg att gtg ttg gga cac aac			9744
Met Leu Asp Leu Val Leu Ala Glu Ala Ser Ile Val Leu Gly His Asn			

3235

3240

3245

ggg tct gac cca gtt ggt ccc gac cgg gcg ttc cag gag ctc gga ttt 9792
 Gly Ser Asp Pro Val Gly Pro Asp Arg Ala Phe Gln Glu Leu Gly Phe
 3250 3255 3260

gat tcg ctg atg gcc gtc gaa ctg cgc aac agg ttg ggc gag gca aca 9840
 Asp Ser Leu Met Ala Val Glu Leu Arg Asn Arg Leu Gly Glu Ala Thr
 3265 3270 3275 3280

gga ttg agt ctg ccg gcc acg ttg atc ttc gat tat ccg agc cca tcc 9888
 Gly Leu Ser Leu Pro Ala Thr Leu Ile Phe Asp Tyr Pro Ser Pro Ser
 3285 3290 3295

gcg ctg gct gag cag ctg gtc ggc gag ctg gtg gga gcg cag ccc gcg 9936
 Ala Leu Ala Glu Gln Leu Val Gly Glu Leu Val Gly Ala Gln Pro Ala
 3300 3305 3310

acc acc gtc gtg gcc ggg gcc gat cca gtg gat gat ccg gtt gtc gtg 9984
 Thr Thr Val Val Ala Gly Ala Asp Pro Val Asp Asp Pro Val Val Val
 3315 3320 3325

gtc gcg atg gga tgc cgg tat ccg ggc gac gtc tgc tcg ccc gag gag 10032
 Val Ala Met Gly Cys Arg Tyr Pro Gly Asp Val Cys Ser Pro Glu Glu
 3330 3335 3340

ctg tgg cag ctg gtt tct gcg gga cgt gat gcg gta tcg acg ttc ccc 10080
 Leu Trp Gln Leu Val Ser Ala Gly Arg Asp Ala Val Ser Thr Phe Pro
 3345 3350 3355 3360

gtc gat cgg ggt tgg gac tgc aac acg ttg ttc gac ccg gat ccg gat 10128
 Val Asp Arg Gly Trp Asp Cys Asn Thr Leu Phe Asp Pro Asp Pro Asp
 3365 3370 3375

cgg gca ggc agt acc tat gtg cga gaa ggt gcc ttc ctg acc ggt gct 10176
 Arg Ala Gly Ser Thr Tyr Val Arg Glu Gly Ala Phe Leu Thr Gly Ala
 3380 3385 3390

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 Asp Arg Phe Asp Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Arg
 3395 3400 3405

gca atg gat ccg cag cag agg ttg ttg ctc gaa gtg gcg tgg gag gtt 10272
 Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Val Ala Trp Glu Val
 3410 3415 3420

ttc gaa cga gca gga atc gct ccg ctg tcg ttg cgg ggt agc agg acc 10320
 Phe Glu Arg Ala Gly Ile Ala Pro Leu Ser Leu Arg Gly Ser Arg Thr

3425	3430	3435	3440	
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Gly Val Phe Ala Gly Thr Asn Gly Gln Asp His Gly Ala Lys Val Ala				
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Ala Ala Pro Glu Ala Ala Gly His Leu Leu Thr Gly Asn Ala Ala Ser				
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gtc ctg gcc ggc cgg ctt tcc tac acg ttc ggc ctt gag ggg cct gcg				10464
Val Leu Ala Gly Arg Leu Ser Tyr Thr Phe Gly Leu Glu Gly Pro Ala				
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gtg gcg gtg gat acc gcg tgt tcg tcg tcg ttg gtg gcg ttg cat ttg				10512
Val Ala Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu				
3490	3495		3500	
gcg tgc cag tcg ctg cgt tcg ggt gag tgt gat atg gcg ttg gca ggt				10560
Ala Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Met Ala Leu Ala Gly				
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Gly Val Thr Val Met Ser Thr Pro Leu Ala Phe Leu Glu Phe Ser Arg				
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Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala				
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Ala Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu				
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cgg ttg tcg gat gct cgt cgg aat ggt cac cgg gtg ttg gcc gtg gtt				10752
Arg Leu Ser Asp Ala Arg Arg Asn Gly His Arg Val Leu Ala Val Val				
3570	3575		3580	
cgc ggg tct gcg gtg aat cag gat ggt gcg tcg aat ggc ctg act gcg				10800
Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala				
3585	3590	3595	3600	
ccg aat ggt ccg tcg cag cag cgg gtg att cgg cag gcc ctc gcg aat				10848
Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Gln Ala Leu Ala Asn				
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gcg ggg ctg tcg gcg tcc gat gtg gat gtc gtg gag gcg cac ggg acc				10896
Ala Gly Leu Ser Ala Ser Asp Val Asp Val Val Glu Ala His Gly Thr				

3620

3625

3630

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 3635 3640 3645

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 Tyr Gly Gln Glu Arg Asp Pro Glu Arg Ala Leu Trp Leu Gly Ser Ile
 3650 3655 3660

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 Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val
 3665 3670 3675 3680

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 Ile Lys Met Val Gln Ala Met Arg His Gly Glu Leu Pro Ala Thr Leu
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 His Val Asp Lys Pro Thr Pro Gln Val Asp Trp Ser Ala Gly Ala Val
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 Arg Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu
 3730 3735 3740

atc ctc gaa caa cca ccg tcg gaa cca gcg gag atc gac caa tcg gat 11280
 Ile Leu Glu Gln Pro Pro Ser Glu Pro Ala Glu Ile Asp Gln Ser Asp
 3745 3750 3755 3760

cgg cgg gtc act gcg cat cca gcg gtg atc ccg tgg atg ttg tcg gct 11328
 Arg Arg Val Thr Ala His Pro Ala Val Ile Pro Trp Met Leu Ser Ala
 3765 3770 3775

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 Arg Ser Leu Ala Ala Leu Gln Ala Gln Ala Ala Ala Leu Gln Ala Arg
 3780 3785 3790

ctg gac cgg ggt cct ggc gct tct ccg ctg gat ttg ggg tat tca ctc 11424
 Leu Asp Arg Gly Pro Gly Ala Ser Pro Leu Asp Leu Gly Tyr Ser Leu
 3795 3800 3805

gcg acc act cgt tct gtg ctg gac gaa cgc gcc gtc gtg tgg ggt gcc 11472
 Ala Thr Thr Arg Ser Val Leu Asp Glu Arg Ala Val Val Trp Gly Ala

3810

3815

3820

gat cgg gag gca ctg ctg tcc agg ctg gca gcg ctc gcc gat ggc cgg 11520
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 3825 3830 3835 3840

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 Thr Ala Pro Gly Val Ile Thr Gly Ser Ala Asn Ser Gly Gly Arg Ile
 3845 3850 3855

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 Gly Phe Val Phe Ser Gly Gln Gly Ser Gln Trp Leu Gly Met Gly Lys
 3860 3865 3870

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 Ala Leu Cys Ala Ala Phe Pro Ala Phe Ala Asp Ala Phe Glu Glu Ala
 3875 3880 3885

tgc gac gcg cta agc gca cac ctg ggc gcg gac gtt cgg ggt gtg ctg 11712
 Cys Asp Ala Leu Ser Ala His Leu Gly Ala Asp Val Arg Gly Val Leu
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 Phe Gly Ala Asp Glu Gln Met Leu Asp Arg Thr Leu Trp Ala Gln Ser
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 3955 3960 3965

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 Val Ala Ala Arg Ala His Leu Met Gln Ala Leu Pro Thr Gly Gly Ala
 3970 3975 3980

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 Met Leu Ala Val Ala Thr Ser Glu Ala Ala Val Gly Pro Leu Leu Ser
 3985 3990 3995 4000

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4005

4010

4015

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 Phe Asp Ala Arg Gly Leu Arg Thr Lys Trp Leu Arg Val Ser His Ala
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 4115 4120 4125

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 Gly Ala Leu Ser Ala Leu Val Glu Gln Cys Leu Ala Gly Ser Asp Gln
 4130 4135 4140

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 4145 4150 4155 4160

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 Val Glu Thr Ala Val Ala Ala Leu Ala His Val His Val Arg Gly Gly
 4165 4170 4175

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 Ala Val Asp Trp Ser Ala Cys Phe Ala Gly Thr Gly Ala Arg Thr Val
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 Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Ala Gly

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Arg Phe Trp Glu Leu Val Glu Arg Ala Asp Pro Glu Pro Leu Val Asp			
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Asp Gln Pro Ala Val Val Ile Asp Ala Leu Ile Ala Arg Gly Ala Glu			
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His Leu Ser Arg Gly Val Ala Ala Thr Val Ile Leu Thr Gln Val Leu			
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Pro Gly Ala Ala Asp Leu Gly Ala Glu Leu Thr Glu Leu Gly Val Lys				
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Val Thr Val Leu Ala Cys Asp Val Thr Asp Arg Asp Glu Leu Ala Ala				
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Val Leu Ala Ala Val Pro Thr Glu Tyr Pro Leu Ser Ala Val Val His				
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Thr Ala Gly Val Gly Thr Pro Ala Asn Leu Ala Glu Thr Thr Leu Ala				

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Gln Phe Ala Asp Val Leu Ser Ala Lys Val Val Gly Ala Ala Asn Leu			
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4770

4775

4780

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<212> PRT

<213> Saccharopolyspora spinosa

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20 25 30

Gln Glu Pro Ile Ala Ile Val Ser Ala Ser Cys Arg Leu Pro Gly Gly
35 40 45

Val Asp Ser Pro Glu Ala Leu Trp Gln Leu Val Arg Thr Gly Thr Asp
50 55 60

Ala Ile Ser Glu Phe Pro Ala Asp Arg Gly Trp Asp Leu Gly Arg Leu
65 70 75 80

Tyr Asp Pro Asp Pro Asn His Gln Gly Thr Ser Tyr Thr Arg Ala Gly
85 90 95

Gly Phe Leu Ala Gly Ala Gly Asp Phe Asp Pro Ala Met Phe Gly Ile
100 105 110

Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
115 120 125

Glu Leu Ser Trp Glu Ala Leu Glu Arg Ala Gly Ile Asp Pro Thr Ser
130 135 140

Leu Arg Gly Ser Lys Thr Gly Val Phe Gly Gly Val Thr Pro Gln Glu
145 150 155 160

Tyr Gly Pro Ser Leu Gln Glu Met Ser Arg Asn Ala Gly Gly Phe Gly
165 170 175

Leu Thr Gly Arg Met Val Ser Val Ala Ser Gly Arg Val Ala Tyr Ser
180 185 190

Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser
195 200 205

Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Ser Gly Glu
210 215 220

Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ala Thr Pro Ala
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Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg
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Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
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Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly
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His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly
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Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val
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Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val Ser Asp Val Asp
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Ala Val Glu Ala His Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile Glu
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Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly Arg Glu Lys Asp Arg
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Pro Asp Ser Gly Arg Pro Cys Arg Val Gly Val Ser Ser Phe Gly Ile
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Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Ser Pro Val Glu Gln
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Val Pro Val Val Pro Trp Val Leu Ser Gly Lys Thr Pro Glu Ala Ala
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Ala Thr Gly Glu Phe Gln Val Asp Pro Leu Leu Asp Gly Val Arg Asp
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740 745 750

Gly Cys Arg Thr Arg Trp Leu Arg Val Ser His Ala Phe His Ser Pro
755 760 765

His Met Glu Pro Met Leu Glu Glu Phe Ala Gln Ile Ser Arg Gly Arg
770 775 780

Glu Tyr His Ala Pro Glu Leu Pro Ile Ile Ser Thr Leu Ile Gly Glu
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Thr Ala Ala Gly Leu Ala Glu Ala Asp His Pro Leu Leu Gly Ala Val
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Val Ala Leu Ala Asp Gly Glu Gly Val Val Leu Thr Gly Arg Leu Thr
 945 950 955 960

Ala Gly Ser His Pro Trp Leu Ser Asp His Arg Val Leu Gly Glu Ile
 965 970 975

Val Val Pro Gly Thr Ala Ile Val Glu Leu Val Trp His Val Gly Glu
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Arg Leu Gly Cys Gly Arg Val Glu Glu Leu Ala Leu Glu Ala Pro Leu
 995 1000 1005

Ile Leu Pro Asp His Gly Ala Val Gln Val Gln Val Leu Val Gly Pro
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Pro Gly Glu Ser Gly Ala Arg Ser Val Ala Leu Tyr Ser Cys Pro Gly
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Glu Ala Ile Glu Pro Glu Trp Lys Lys His Ala Thr Gly Val Leu Leu
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 Pro Pro Val Ala Ala Glu Asn His Glu Leu Thr Ala Trp Pro Pro Glu
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 1075 1080 1085
 His Gly Phe Ala Tyr Gly Pro Ala Phe Arg Cys Leu Arg Gly Ala Trp
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 Gln Ala Gly Val Asp Arg Phe Gly Val His Pro Ala Leu Leu Asp Ala
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 Val Leu His Ala Ala Ala Glu Thr Ser Val Val Gln Ser Glu Ala
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 Gly Asp Cys Leu Phe Glu Val Glu Trp His Arg Lys Ala Leu Leu Gly
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 Thr Thr Ala Gly Asp Asp Leu Ala Ile Val Gly Asp Gly Pro Ser Trp
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Ala Val Ser Ala Asp Ser Asp Ser Asp Val Ala Asp Leu Val Gly Ala
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Ser Ser Trp Gly Leu Leu Ser Ser Ala Gln Ser Glu Asn Pro Gly Arg
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Phe Val Leu Val Asp Val Asp Gly Thr Pro Glu Ser Trp Gln Ala Leu
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Pro Ala Ala Val Arg Ala Gly Glu Pro Gln Leu Ala Leu Arg Arg Gly
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1395 1400 1405

Ser Ser Pro Gln Leu Asp Thr Asp Gly Thr Val Leu Ile Thr Gly Gly
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Thr Gly Ala Leu Gly Gly Val Val Ala Arg His Leu Val Glu Glu His
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Gly Ile Arg Arg Leu Val Leu Ala Gly Arg Arg Gly Trp Asn Ala Pro
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Gly Val His Glu Leu Val Asp Glu Leu Ala Arg Ala Gly Ala Val Val
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Val Val Ala Cys Asp Val Ala Asp Arg Thr Asp Leu Glu His Val
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Ala Gly Val Leu Ala Asp Gly Val Ile Gly Ser Leu Ser Ala Ala Asp
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Val Gly Thr Val Phe Ala Pro Lys Val Thr Gly Ala Trp His Leu His
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Asn Thr Phe Leu Asp Ala Leu Ala Arg Tyr Arg Arg Ala Arg Gly Leu
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Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
1860 1865 1870

Leu Leu Leu Glu Val Ala Trp Glu Thr Leu Glu Arg Ala Gly Ile Asp
1875 1880 1885

Pro Phe Ser Leu His Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met
890 1895 1900

His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly Phe
905 1910 1915 1920

Glu Gly His Leu Gly Thr Gly Asn Ala Gly Ser Val Leu Ser Gly Arg
1925 1930 1935

Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr
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1955 1960 1965

Arg Ala Gly Glu Cys Glu Phe Ala Leu Ala Gly Gly Val Thr Val Met
1970 1975 1980

Thr Pro Thr Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala
1985 1990 1995 2000

Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly
2005 2010 2015

Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala
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 Glu Leu Glu Glu Ala His Glu Arg Leu His Glu Leu Glu Arg Gln Glu
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 Phe Asp Pro Asp Pro Gly Arg Ala Gly Thr Ser Tyr Val Arg Glu Gly
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 Gly Phe Leu Arg Gly Val Ala Asp Phe Asp Ala Gly Leu Phe Gly Ile

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gcc acc ggc aac gcg ggc agc gtc gca tcc ggc cgg gtg gct tac acc			576
Ala Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Thr			
180	185	190	
ttc ggg tta gag ggc ccg gcg gtc acc gtg gac acc gcc tgc tcg tcg			624
Phe Gly Leu Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser			
195	200	205	
tcc ctg gtg gcg ctg cac ctg gcc tgc cag tcc ctg cgg ctg ggc gaa			672
Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Leu Gly Glu			
210	215	220	
tgc gac ctg gcc ctg gcc ggt ggc att tcg gtg atg gcc acg ccg gga			720
Cys Asp Leu Ala Leu Ala Gly Gly Ile Ser Val Met Ala Thr Pro Gly			
225	230	235	240
gcc ttc gtc gag ttc agc cgg caa cgc gca ctc gcc tcg gat ggc cgg			768
Ala Phe Val Glu Phe Ser Arg Gln Arg Ala Leu Ala Ser Asp Gly Arg			
245	250	255	
tgc aag ccc ttc gcg gat gcc gcc gac ggc acc ggc tgg ggc gag ggc			816
Cys Lys Pro Phe Ala Asp Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly			
260	265	270	
gcc gga atg ctg ctg ctg gaa cgg ctg tcg gac gca cga cga aac ggc			864
Ala Gly Met Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly			
275	280	285	
cac ccg gtg ctg gcg gcg gtg gtc ggt tcc gcg atc aac cag gac ggc			912
His Pro Val Leu Ala Ala Val Val Gly Ser Ala Ile Asn Gln Asp Gly			

290	295	300	
acg tcc aac ggc ctg acc gcg ccc agc ggt ccc gca cag cag cga gtg			960
Thr Ser Asn Gly Leu Thr Ala Pro Ser Gly Pro Ala Gln Gln Arg Val			
305	310	315	320
atc cgc caa gcc ctg gcg aac gcc ggg ttg tcg ccc gcc gag gtc gat			1008
Ile Arg Gln Ala Leu Ala Asn Ala Gly Leu Ser Pro Ala Glu Val Asp			
325	330		335
gtg gtc gag gcg cac ggc acg ggc acg gcc ttg ggc gac ccg atc gag			1056
Val Val Glu Ala His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu			
340	345		350
gcg cag gcc ctg atc gcc acc tac ggg gcg aac cgg tcg gcg gat cat			1104
Ala Gln Ala Leu Ile Ala Thr Tyr Gly Ala Asn Arg Ser Ala Asp His			
355	360		365
ccg ctg ctg ctg ggt tcc ctc aag tcg aac atc ggc cac acc cag gct			1152
Pro Leu Leu Leu Gly Ser Leu Lys Ser Asn Ile Gly His Thr Gln Ala			
370	375		380
gcc gcc ggt gtg gcc ggg gtg atc aag tcg gtc ctg gcc atc agg cac			1200
Ala Ala Gly Val Ala Gly Val Ile Lys Ser Val Leu Ala Ile Arg His			
385	390	395	400
cgg gag atg ccc cgc agc ctg cac atc gac cag cca tcg cag cac gtg			1248
Arg Glu Met Pro Arg Ser Leu His Ile Asp Gln Pro Ser Gln His Val			
405	410		415
gac tgg tcg gcg ggc gcg gtg cgg ctg ctc acg gac agc gtt gac tgg			1296
Asp Trp Ser Ala Gly Ala Val Arg Leu Leu Thr Asp Ser Val Asp Trp			
420	425		430
ccg gat ctc ggc agg ccg cgc cga gca ggg gtg tcc tcg ttc ggc atg			1344
Pro Asp Leu Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Met			
435	440		445
agc ggt acc aac gca cac ctg atc gtc gag gaa gta tcc gac gag ccg			1392
Ser Gly Thr Asn Ala His Leu Ile Val Glu Glu Val Ser Asp Glu Pro			
450	455		460
gtc tcg ggc agt acc gag ccg acc ggg gca ttt ccc tgg ccg ctg tcc			1440
Val Ser Gly Ser Thr Glu Pro Thr Gly Ala Phe Pro Trp Pro Leu Ser			
465	470	475	480
ggc aag acg gag acg gca ttg cgc gag cag gct gcc gag ttg ctc tcc			1488
Gly Lys Thr Glu Thr Ala Leu Arg Glu Gln Ala Ala Glu Leu Leu Ser			

485	490	495	
gta gtg acc gag cac ccg gag ccg gga ctg ggg gac gtc ggg tac tcg			1536
Val Val Thr Glu His Pro Glu Pro Gly Leu Gly Asp Val Gly Tyr Ser			
500	505	510	
ctg gcc acc ggt cgc gct gcg atg gag cac cgg gct gtc gtg gtt gcc			1584
Leu Ala Thr Gly Arg Ala Ala Met Glu His Arg Ala Val Val Val Ala			
515	520	525	
gac gat cgg gac tct ttc gtc gcc gga ctg acg gcg ttg gct gcg ggc			1632
Asp Asp Arg Asp Ser Phe Val Ala Gly Leu Thr Ala Leu Ala Ala Gly			
530	535	540	
gtt ccg gca gcc aac gtg gtg cag ggc gcg gcc gac tgc aag gga aag			1680
Val Pro Ala Ala Asn Val Val Gln Gly Ala Ala Asp Cys Lys Gly Lys			
545	550	555	560
gtc gcg ttc gtg ttc ccc ggc cag ggc tcg cat tgg cag ggg atg gcg			1728
Val Ala Phe Val Phe Pro Gly Gln Gly Ser His Trp Gln Gly Met Ala			
565	570	575	
agg gaa ctg tcc gaa tcc tcg ccg gtg ttc cgg cgg aag ctg gcg gaa			1776
Arg Glu Leu Ser Glu Ser Ser Pro Val Phe Arg Arg Lys Leu Ala Glu			
580	585	590	
tgc gcg gcg gct acg gcc cct tac gtg gac tgg tcg ctg ctc ggc gtc			1824
Cys Ala Ala Ala Thr Ala Pro Tyr Val Asp Trp Ser Leu Leu Gly Val			
595	600	605	
ctt cgc ggt gat ccc gat gca ccc gcg ctg gat cgc gac gac gtg att			1872
Leu Arg Gly Asp Pro Asp Ala Pro Ala Leu Asp Arg Asp Asp Val Ile			
610	615	620	
cag ctc gcg ctg ttc gcc atg atg gtg tcg ctg gcc gaa ctg tgg cgt			1920
Gln Leu Ala Leu Phe Ala Met Met Val Ser Leu Ala Glu Leu Trp Arg			
625	630	635	640
tcg tgc gga gtg gag ccc gcc gcg gtg gtc ggt cat tcc cag ggc gag			1968
Ser Cys Gly Val Glu Pro Ala Ala Val Val Gly His Ser Gln Gly Glu			
645	650	655	
atc gcc gcc gcc cat gtg gca ggc gct ttg tcc ttg act gat gcg gtg			2016
Ile Ala Ala Ala His Val Ala Gly Ala Leu Ser Leu Thr Asp Ala Val			
660	665	670	
cgc atc atc gct gcc cgc tgc gat gcg gtg tcg gcg ctg acc ggg aag			2064
Arg Ile Ile Ala Ala Arg Cys Asp Ala Val Ser Ala Leu Thr Gly Lys			

675

680

685

gga ggc atg ctc gcg att gcc ttg ccg gaa agc gcg gtg gtg aag cga 2112
 Gly Gly Met Leu Ala Ile Ala Leu Pro Glu Ser Ala Val Val Lys Arg
 690 695 700

atc gca ggc ctg ccg gag ctg acc gtt gcg gcg gtc aac gga ccc ggc 2160
 Ile Ala Gly Leu Pro Glu Leu Thr Val Ala Ala Val Asn Gly Pro Gly
 705 710 715 720

tcc act gtc gtt tcc ggc gaa ccg tcg gct ctg gag cgt ctg cag acc 2208
 Ser Thr Val Val Ser Gly Glu Pro Ser Ala Leu Glu Arg Leu Gln Thr
 725 730 735

gaa ctg acc gcg gaa aac gtg cag acc ccg ccg gtg gga att gat tac 2256
 Glu Leu Thr Ala Glu Asn Val Gln Thr Arg Arg Val Gly Ile Asp Tyr
 740 745 750

gcc tcg cat tcg ccg cag atc gcg cag gtc cag ggc ccg ctt ctg gac 2304
 Ala Ser His Ser Pro Gln Ile Ala Gln Val Gln Gly Arg Leu Leu Asp
 755 760 765

cgg ctg ggc gaa gtc ggg tcc gaa cct gct gag atc gct ttc tac tcg 2352
 Arg Leu Gly Glu Val Gly Ser Glu Pro Ala Glu Ile Ala Phe Tyr Ser
 770 775 780

acg gtc acc ggc gag ccg acg gac acc ggc cga ctc gac gcc gac tac 2400
 Thr Val Thr Gly Glu Arg Thr Asp Thr Gly Arg Leu Asp Ala Asp Tyr
 785 790 795 800

tgg tac cag aac ctt ccg cag ccc gtc cgc ttc cag cag acc gtc gcc 2448
 Trp Tyr Gln Asn Leu Arg Gln Pro Val Arg Phe Gln Gln Thr Val Ala
 805 810 815

cgg atg gca gat cag ggc tat ccg ttc ttc gtc gag gtg agc ccg cac 2496
 Arg Met Ala Asp Gln Gly Tyr Arg Phe Phe Val Glu Val Ser Pro His
 820 825 830

ccg ctg ctc acc gcc gga atc cag gaa acg ctg gaa gcc gcg gac gcg 2544
 Pro Leu Leu Thr Ala Gly Ile Gln Glu Thr Leu Glu Ala Ala Asp Ala
 835 840 845

ggc ggg gtg gtg gtc ggt tcg ctg ccg cgt gcc gag gcc gcc tcc ccg 2592
 Gly Gly Val Val Val Gly Ser Leu Arg Arg Gly Glu Gly Gly Ser Arg
 850 855 860

cgc tgg ctg act tcg ctg gcc gag tgc cag gtg cgc gga ctg ccg gtg 2640
 Arg Trp Leu Thr Ser Leu Ala Glu Cys Gln Val Arg Gly Leu Pro Val

865	870	875	880	
aat tgg gaa cag gta ttc ctc aac acc gga gcc cga cgc gtg ccg ctg				2688
Asn Trp Glu Gln Val Phe Leu Asn Thr Gly Ala Arg Arg Val Pro Leu				
	885	890	895	
ccg acc tac ccg ttc cag cgg cag cgg tac tgg ttg gag tcc gcc gag				2736
Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Glu Ser Ala Glu				
	900	905	910	
tac gac gcg ggc gat ctc ggt tgc gtg ggc ttg ctc tcc gcc gag cat				2784
Tyr Asp Ala Gly Asp Leu Gly Ser Val Gly Leu Leu Ser Ala Glu His				
	915	920	925	
ccc ctg ctc ggg gct gcg gtg acg ctg gcc gat gcg ggc ggg ttc ctg				2832
Pro Leu Leu Gly Ala Ala Val Thr Leu Ala Asp Ala Gly Gly Phe Leu				
	930	935	940	
ctg acc ggc aag ctg tgc gtc aag acc cag ccc tgg ttg gcc gac cac				2880
Leu Thr Gly Lys Leu Ser Val Lys Thr Gln Pro Trp Leu Ala Asp His				
	945	950	955	960
gtg gtc ggc ggg gcg atc ctg ctg ccc ggc acc gcg ttc gtg gaa atg				2928
Val Val Gly Gly Ala Ile Leu Leu Pro Gly Thr Ala Phe Val Glu Met				
	965	970	975	
ctg ata cgc gcc gcg gac cag gtc ggg tgc gat ctg atc gag gag ttg				2976
Leu Ile Arg Ala Ala Asp Gln Val Gly Cys Asp Leu Ile Glu Glu Leu				
	980	985	990	
tcc ctg acg act ccg ctg gtt ttg ccc gcg acc ggt gcg gtg cag gtg				3024
Ser Leu Thr Thr Pro Leu Val Leu Pro Ala Thr Gly Ala Val Gln Val				
	995	1000	1005	
cag atc gcg gtt ggc ggt ccg gac gag gcc ggg cgc cgc tgc gtc cgc				3072
Gln Ile Ala Val Gly Gly Pro Asp Glu Ala Gly Arg Arg Ser Val Arg				
	1010	1015	1020	
gtg cat tcc tgt cga gac gac gcc gtg ccg cag gac tgc tgg acc tgc				3120
Val His Ser Cys Arg Asp Asp Ala Val Pro Gln Asp Ser Trp Thr Cys				
	1025	1030	1035	1040
cac gcg acc ggc acg ttg acc tcc agc gat cac cag gac gcc ggc cag				3168
His Ala Thr Gly Thr Leu Thr Ser Ser Asp His Gln Asp Ala Gly Gln				
	1045	1050	1055	
ggc ccc gat ggg att tgg ccg ccc aac gat gct gtc gcg gtt ccg ctg				3216
Gly Pro Asp Gly Ile Trp Pro Pro Asn Asp Ala Val Ala Val Pro Leu				

1060

1065

1070

gac agc ttc tac gcc cgc gca gct gag cgg ggc ttc gat ttc ggc ccg 3264
 Asp Ser Phe Tyr Ala Arg Ala Ala Glu Arg Gly Phe Asp Phe Gly Pro
 1075 1080 1085

gcg ttc cag ggg ttg cag gcg gct tgg aag cgc gga gac gag atc ttc 3312
 Ala Phe Gln Gly Leu Gln Ala Ala Trp Lys Arg Gly Asp Glu Ile Phe
 1090 1095 1100

gcc gag gtc ggc ctg ccc acc gca cac cgc gaa gac gcc ggc agg ttc 3360
 Ala Glu Val Gly Leu Pro Thr Ala His Arg Glu Asp Ala Gly Arg Phe
 1105 1110 1115 1120

gga atc cac cct gct ctg ctg gat gcg gca ctg cag gcg ctg ggc gca 3408
 Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu Gln Ala Leu Gly Ala
 1125 1130 1135

gcc gaa gag gat ccg gac gag gga tgg ctc ccg ttc gcg tgg caa ggt 3456
 Ala Glu Glu Asp Pro Asp Glu Gly Trp Leu Pro Phe Ala Trp Gln Gly
 1140 1145 1150

gtg tcc ctc aaa gcg acg ggc gca ctt tcc ctt cgg gtg cac ctc gtt 3504
 Val Ser Leu Lys Ala Thr Gly Ala Leu Ser Leu Arg Val His Leu Val
 1155 1160 1165

ccg gcg ggc gcg aat gcg gtg tcg gtg ttc acg acc gac acg act ggc 3552
 Pro Ala Gly Ala Asn Ala Val Ser Val Phe Thr Thr Asp Thr Thr Gly
 1170 1175 1180

caa gcc gtg ctc tcc atc gat tcg ctg gtg ctg cgc cag att tcg gac 3600
 Gln Ala Val Leu Ser Ile Asp Ser Leu Val Leu Arg Gln Ile Ser Asp
 1185 1190 1195 1200

aag cag ttg gca gcg gcc cgt gcg atg gaa cac gag tcc ctg ttc ccg 3648
 Lys Gln Leu Ala Ala Ala Arg Ala Met Glu His Glu Ser Leu Phe Arg
 1205 1210 1215

gtc gac tgg aag cga atc tcg ccc ggc gct gcc aag ccg gtc tcc tgg 3696
 Val Asp Trp Lys Arg Ile Ser Pro Gly Ala Ala Lys Pro Val Ser Trp
 1220 1225 1230

gca gtg atc ggc aat gac gaa ctc gcc cga gcc tgc ggc tcg gca ctt 3744
 Ala Val Ile Gly Asn Asp Glu Leu Ala Arg Ala Cys Gly Ser Ala Leu
 1235 1240 1245

ggc acg gaa ctc cac ccc gac ctg acc ggg ttg gct gac ccg ccc ccg 3792
 Gly Thr Glu Leu His Pro Asp Leu Thr Gly Leu Ala Asp Pro Pro Pro

1250	1255	1260	
gac gtc gtg gtg gtg cca tgc ggt gcg tct cgc cag gac ttg gac gtt			3840
Asp Val Val Val Val Pro Cys Gly Ala Ser Arg Gln Asp Leu Asp Val			
1265	1270	1275	1280
gct tcc gag gca cgt gcc gcg aca caa cgc atg ctt gac ctg atc cag			3888
Ala Ser Glu Ala Arg Ala Ala Thr Gln Arg Met Leu Asp Leu Ile Gln			
	1285	1290	1295
gat tgg ttg gcg gcg gcg cga ttc gcc gga tct cgc ctg gtg gtt gtg			3936
Asp Trp Leu Ala Ala Ala Arg Phe Ala Gly Ser Arg Leu Val Val Val			
	1300	1305	1310
acg tgt ggt gcg gcg tcg aca ggt ccc gcc gag ggt gtt tcc gac ctg			3984
Thr Cys Gly Ala Ala Ser Thr Gly Pro Ala Glu Gly Val Ser Asp Leu			
	1315	1320	1325
gtg cat gct gcg tcg tgg ggt ttg ttg cgt tcg gcg cag tcg gag aac			4032
Val His Ala Ala Ser Trp Gly Leu Leu Arg Ser Ala Gln Ser Glu Asn			
	1330	1335	1340
ccg gac cga ttc gtg ttg gtc gat gtg gac gga acc gcc gaa tca tgg			4080
Pro Asp Arg Phe Val Leu Val Asp Val Asp Gly Thr Ala Glu Ser Trp			
	1345	1350	1355
			1360
cgt gcg ctc gcg gcg gcc gtg cgt tcc gga gaa ccg cag ctg gcg ttg			4128
Arg Ala Leu Ala Ala Ala Val Arg Ser Gly Glu Pro Gln Leu Ala Leu			
	1365	1370	1375
cgc gcc ggt gaa gtc cgg gtg cct cgc ctg gcg cga tgt gtt gcc gcc			4176
Arg Ala Gly Glu Val Arg Val Pro Arg Leu Ala Arg Cys Val Ala Ala			
	1380	1385	1390
gag gac agc cgg atc cca gtg ccc ggt gcg gat ggg acg gtg ttg att			4224
Glu Asp Ser Arg Ile Pro Val Pro Gly Ala Asp Gly Thr Val Leu Ile			
	1395	1400	1405
tcc ggc ggt acg ggc ctg ctg ggc ggg ttg gtt gcc cgg cat ttg gtg			4272
Ser Gly Gly Thr Gly Leu Leu Gly Gly Leu Val Ala Arg His Leu Val			
	1410	1415	1420
gcg gag cgc ggt gtc cgc cgc ctg gtg ctc gcg ggg cga cgc ggc tgg			4320
Ala Glu Arg Gly Val Arg Arg Leu Val Leu Ala Gly Arg Arg Gly Trp			
	1425	1430	1435
			1440
agc gcc ccc ggg gtc acc gac ctg gtg gat gag ttg gtg ggc ctg gga			4368
Ser Ala Pro Gly Val Thr Asp Leu Val Asp Glu Leu Val Gly Leu Gly			

1440

1450

1455

gct gcg gtc gag gtg gcg agc tgc gat gtc ggg gat cgg gcc cag ttg 4416
 Ala Ala Val Glu Val Ala Ser Cys Asp Val Gly Asp Arg Ala Gln Leu
 1460 1465 1470

gac cgg ctg ctg acg acg atc tgc gca gag ttc ccg ctg cgc gga gtg 4464
 Asp Arg Leu Leu Thr Thr Ile Ser Ala Glu Phe Pro Leu Arg Gly Val
 1475 1480 1485

gtg cat gcg gcc ggg gca ctt gcc gac ggg gtc gtc gag tgc ctg aca 4512
 Val His Ala Ala Gly Ala Leu Ala Asp Gly Val Val Glu Ser Leu Thr
 1490 1495 1500

cca gag cac gtg gca aag gtg ttc ggc ccg aag gcc gcc ggt gcg tgg 4560
 Pro Glu His Val Ala Lys Val Phe Gly Pro Lys Ala Ala Gly Ala Trp
 1505 1510 1515 1520

cac ctg cac gag ttg act ctt gat ctg gat ctc tgc ttc ttc gtg ctc 4608
 His Leu His Glu Leu Thr Leu Asp Leu Asp Leu Ser Phe Phe Val Leu
 1525 1530 1535

ttc tcc tgc ttc tcc ggc gtg gcg ggg gct gcg ggt cag gga aac tac 4656
 Phe Ser Ser Phe Ser Gly Val Ala Gly Ala Ala Gly Gln Gly Asn Tyr
 1540 1545 1550

gcg gcg gcg aac gcg ttc ctg gac ggc ctg gct cag cac cgg cgg acg 4704
 Ala Ala Ala Asn Ala Phe Leu Asp Gly Leu Ala Gln His Arg Arg Thr
 1555 1560 1565

gcg ggg ctg cct gcg gtg tgc ctg gct tgg ggc ttg tgg gag cag ccc 4752
 Ala Gly Leu Pro Ala Val Ser Leu Ala Trp Gly Leu Trp Glu Gln Pro
 1570 1575 1580

agc ggg atg acc gga gcg ctc gat gcg gcg ggc cgt agc cgc att gcg 4800
 Ser Gly Met Thr Gly Ala Leu Asp Ala Ala Gly Arg Ser Arg Ile Ala
 1585 1590 1595 1600

cgc acc aat ccg ccg atg tcc gcg ccg gac ggg ttg cgg ctg ttc gag 4848
 Arg Thr Asn Pro Pro Met Ser Ala Pro Asp Gly Leu Arg Leu Phe Glu
 1605 1610 1615

atg gcg ttt cgc gtt ccg ggc gaa tgc ctt ctg gtt ccg gtc cac gtc 4896
 Met Ala Phe Arg Val Pro Gly Glu Ser Leu Leu Val Pro Val His Val
 1620 1625 1630

gac ctg aac gcc ctg cgc gct gat gcg gcc gac ggc ggt gtg cct gcg 4944
 Asp Leu Asn Ala Leu Arg Ala Asp Ala Ala Asp Gly Gly Val Pro Ala

1635	1640	1645	
ttg ttg cgc gac ctg gtg cca gcg ccc gtg cgg cgg agc gcg gtc aac			4992
Leu Leu Arg Asp Leu Val Pro Ala Pro Val Arg Arg Ser Ala Val Asn			
1650	1655	1660	
gag tcg gcg gac gtc aac ggt ctg gtt ggt cgg ctg cgg agg ctg ccg			5040
Glu Ser Ala Asp Val Asn Gly Leu Val Gly Arg Leu Arg Arg Leu Pro			
1665	1670	1675	1680
gac ctg gat cag gaa acc cag ctg ttg ggt ttg gtg cgc gag cat gtt			5088
Asp Leu Asp Gln Glu Thr Gln Leu Leu Gly Leu Val Arg Glu His Val			
1685	1690	1695	
tcg gcg gtg ctg ggg cat tcg ggt gcg gtc gag gtc ggg gcc gat cgt			5136
Ser Ala Val Leu Gly His Ser Gly Ala Val Glu Val Gly Ala Asp Arg			
1700	1705	1710	
gct ttc cgg gat ttg ggt ttt gat tcg ttg tcc ggt gtg gag ttt cgg			5184
Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Phe Arg			
1715	1720	1725	
aac cgg ctt ggc ggg gtg ctg ggc gtt cgg ttg ccg gct act gcg gtg			5232
Asn Arg Leu Gly Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val			
1730	1735	1740	
ttc gac tat ccg aca ccg cgg gcg ttg gtt cgg ttc ttg ctc gac aaa			5280
Phe Asp Tyr Pro Thr Pro Arg Ala Leu Val Arg Phe Leu Leu Asp Lys			
1745	1750	1755	1760
ctg att ggt ggc gtg gag gct ccg act ccc gca ccg gcg gct gtg gcg			5328
Leu Ile Gly Gly Val Glu Ala Pro Thr Pro Ala Pro Ala Ala Val Ala			
1765	1770	1775	
gcg gtg act gct gac gat ccc gtt gtg atc gtg ggg atg ggc tgt cgt			5376
Ala Val Thr Ala Asp Asp Pro Val Val Ile Val Gly Met Gly Cys Arg			
1780	1785	1790	
tat ccg ggt ggg gtg tcc tcg ccg gag gag ctt tgg cgt ttg gtg gcc			5424
Tyr Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala			
1795	1800	1805	
ggg ggc ttg gat gcg gtg gcg gag ttc ccg gac gat cgt ggc tgg gat			5472
Gly Gly Leu Asp Ala Val Ala Glu Phe Pro Asp Asp Arg Gly Trp Asp			
1810	1815	1820	
cag gcg ggg ttg ttc gat ccg gat ccc gat cgt ctt ggg acc tcg tat			5520
Gln Ala Gly Leu Phe Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr			

1825	30	1835	1840
gtg tgt gag ggt ggc ttc ctg cga gat gcg gca gag ttc gat gcc ggt			5568
Val Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Gly			
1845	1850	1855	
ttc ttc ggg att tcc ccg cgt gag gcg ttg gcg atg gat ccg cag cag			5616
Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln			
1860	1865	1870	
cgg ttg ctg ctg gaa gtc gct tgg gaa acc gtg gag cgg gcg ggg att			5664
Arg Leu Leu Leu Glu Val Ala Trp Glu Thr Val Glu Arg Ala Gly Ile			
1875	1880	1885	
gat ccg ctt tcg ttg cgg ggg agc cgg acc ggc gtg ttc gcg ggg ctg			5712
Asp Pro Leu Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu			
1890	1895	1900	
atg cac cac gac tac ggc gcg cgg ttc atc acg agg gcg ccg gag ggt			5760
Met His His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly			
1905	1910	1915	1920
ttc gag ggt tat cta ggt aat ggc agc gcg gga ggc gtg ttt tcg ggt			5808
Phe Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Gly Val Phe Ser Gly			
1925	1930	1935	
cgg gtt gcg tat tcg ttt ggt ttc gag ggt cct gcg gtg acg gtg gat			5856
Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp			
1940	1945	1950	
acg gcg tgt tcg tcg tcg ttg gtg gcg ctg cac ctg gcg ggt caa gca			5904
Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala			
1955	1960	1965	
ctg cgg tct ggt gag tgt gat ctg gct ctt gcg ggt ggt gtg acg gtg			5952
Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val			
1970	1975	1980	
atg gcc acg ccg ggg atg ttc gtg gag ttt tcg cgt caa cgg ggc ttg			6000
Met Ala Thr Pro Gly Met Phe Val Glu Phe Ser Arg Gln Arg Gly Leu			
1985	1990	1995	2000
gcg gcg gat ggg cgg tgc aag tcg ttt gcg gcg gct gcg gat ggc acc			6048
Ala Ala Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr			
2005	2010	2015	
ggt tgg gga gaa ggc gcg ggc ttg gtg ttg ttg gag cgg ctg tcg gat			6096
Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp			

2020	2025	2030	
gcc cgg cgc aac ggg cac gcg gtt ctg gcg gtc gtg cgg ggt agc gcg Ala Arg Arg Asn Gly His Ala Val Leu Ala Val Val Arg Gly Ser Ala 2035 2040 2045			6144
gtg aat cag gat ggt gcg tcg aat ggt ttg acg gcg ccg aat ggg ccc Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro 2050 2055 2060			6192
tcg cag cag cgg gtg atc acg cag gcg ttg gcg agt gct ggt ttg tcg Ser Gln Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser 2065 2070 2075 2080			6240
gtg tct gat gtg gac gcc gtg gag gcg cat ggg act gga acc agg ctt Val Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu 2085 2090 2095			6288
ggg gat ccg att gag gcg cag gct ctg att gcc act tac ggg cag ggg Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly 2100 2105 2110			6336
cgg gat agc gat cgg ccg ttg tgg ttg ggg tcg gtg aag tcg aat att Arg Asp Ser Asp Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile 2115 2120 2125			6384
ggg cat acg cag gcg gcg gcg ggt gtc gct ggt gtg atc aag atg gtg Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val 2130 2135 2140			6432
atg gcg atg cgg cac ggg cag ctg ccc gcg acg ttg cat gtg gat gaa Met Ala Met Arg His Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu 2145 2150 2155 2160			6480
cct acg tcg gaa gtg gat tgg tcg gcg ggg gat gtc cag ctc ctc acg Pro Thr Ser Glu Val Asp Trp Ser Ala Gly Asp Val Gln Leu Leu Thr 2165 2170 2175			6528
gag aac acc ccc tgg ccc ggc aac agc cat cct cgg cgg gtg ggc gtg Glu Asn Thr Pro Trp Pro Gly Asn Ser His Pro Arg Arg Val Gly Val 2180 2185 2190			6576
tcg tcg ttc ggg atc agc ggc acc aac gca cac gtc atc ctc gaa caa Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln 2195 2200 2205			6624
gcc tcg aaa aca cca gac gag act gcg gac aag agc ggt ccc gat tcg Ala Ser Lys Thr Pro Asp Glu Thr Ala Asp Lys Ser Gly Pro Asp Ser			6672

2210	2215	2220	
gaa tcg acc gtg gac ctt cca gcg gtc ccg ttg atc gtg tcg ggg aga			6720
Glu Ser Thr Val Asp Leu Pro Ala Val Pro Leu Ile Val Ser Gly Arg			
2225	2230	2235	2240
aca ccg gca gcg ctc agc gct cag gcg agc gca ttg ttg tcc tat ttg			6768
Thr Pro Ala Ala Leu Ser Ala Gln Ala Ser Ala Leu Leu Ser Tyr Leu			
2245	2250		2255
ggt gag cgt ggc gat att tcc acg ctg gat gcg gcg ttt tcg ttg gct			6816
Gly Glu Arg Gly Asp Ile Ser Thr Leu Asp Ala Ala Phe Ser Leu Ala			
2260	2265		2270
tcc tcc cgg gcc gcg ttg gag gag ccg gcg gtg gtg ctg gga gcg gac			6864
Ser Ser Arg Ala Ala Leu Glu Glu Arg Ala Val Val Leu Gly Ala Asp			
2275	2280		2285
cgc gaa acg ttg ttg tcc ggg ttg gaa gcg ctg gct tcc ggt cgc gag			6912
Arg Glu Thr Leu Leu Ser Gly Leu Glu Ala Leu Ala Ser Gly Arg Glu			
2290	2295		2300
gct tct ggg gtg gtg tcg gga tcc ccg gtc tct ggc ggg gtt ggg ttc			6960
Ala Ser Gly Val Val Ser Gly Ser Pro Val Ser Gly Gly Val Gly Phe			
2305	2310	2315	2320
gtg ttc gcc ggt cag ggc gga cag tgg ttg ggg atg ggc ccg ggg ctc			7008
Val Phe Ala Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu			
2325	2330		2335
tac tcg gtt ttt ccg gtg ttc gct gac gcg ttt gac gaa gca tgt gcc			7056
Tyr Ser Val Phe Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala			
2340	2345		2350
gga ctg gac gcg cat ctg ggg cag gac gtg ggg gtc ccg gat gtg gtg			7104
Gly Leu Asp Ala His Leu Gly Gln Asp Val Gly Val Arg Asp Val Val			
2355	2360		2365
ttt ggt tcc gac ggg tcc ttg ttg gat ccg acg ctg tgg gcc cag tcg			7152
Phe Gly Ser Asp Gly Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser			
2370	2375		2380
ggt ttg ttc gcg ttg cag gtt ggt ttg ctg agc ctg ctg ggt tcg tgg			7200
Gly Leu Phe Ala Leu Gln Val Gly Leu Leu Ser Leu Leu Gly Ser Trp			
2385	2390	2395	2400
ggt gtc ccg ccg ggt gtg gtg ctg ggc cat tcg gtc ggc gag ttc gcg			7248
Gly Val Arg Pro Gly Val Val Leu Gly His Ser Val Gly Glu Phe Ala			

2405	2410	2415	
gcg gcg gtt gcg gcg gga gtg ttg tcg ttg ccg gat gcg gct cgg atg			7296
Ala Ala Val Ala Ala Gly Val Leu Ser Leu Pro Asp Ala Ala Arg Met			
2420	2425	2430	
gtg gcg ggt cgt gcc cgg ttg atg cag gcg ttg cct tct ggc ggt gcc			7344
Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala			
2435	2440	2445	
atg ttg gcg gtg gct gct ggt gag gag cag ctg cgg ccg ttg ttg gcc			7392
Met Leu Ala Val Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala			
2450	2455	2460	
gat cgg gtt gat ggt gcg ggt atc gcc gcg gtc aac gct cct gag tcg			7440
Asp Arg Val Asp Gly Ala Gly Ile Ala Ala Val Asn Ala Pro Glu Ser			
2465	2470	2475	2480
gtg gtg ctc tcc ggc gat cgg gag gtg ctt gac gac atc gcc ggc gcg			7488
Val Val Leu Ser Gly Asp Arg Glu Val Leu Asp Asp Ile Ala Gly Ala			
2485	2490	2495	
ctg gat ggg caa ggg att cgg tgg cgg cgg ttg cgg gtt tcg cat gcg			7536
Leu Asp Gly Gln Gly Ile Arg Trp Arg Arg Leu Arg Val Ser His Ala			
2500	2505	2510	
ttt cat tcg tat cgg atg gac ccg atg ttg cag gag ttc gcc gaa atc			7584
Phe His Ser Tyr Arg Met Asp Pro Met Leu Gln Glu Phe Ala Glu Ile			
2515	2520	2525	
gca cgc agc gtg gac tac cgg cgt ggc gac cta ccg gtc gtg tcg acg			7632
Ala Arg Ser Val Asp Tyr Arg Arg Gly Asp Leu Pro Val Val Ser Thr			
2530	2535	2540	
ttg acg ggt gag ctc gac acc gca ggt gtg atg gct acg ccg gag tat			7680
Leu Thr Gly Glu Leu Asp Thr Ala Gly Val Met Ala Thr Pro Glu Tyr			
2545	2550	2555	2560
tgg gtg cgt cag gtt cga gag ccc gtc cgc ttc gcc gac ggc gtc cgg			7728
Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Arg			
2565	2570	2575	
gtg ctc gcg cag caa ggg gtc gcc acg atc ttc gaa ctc ggc cct gat			7776
Val Leu Ala Gln Gln Gly Val Ala Thr Ile Phe Glu Leu Gly Pro Asp			
2580	2585	2590	
gcg acg ctg tcg gcc ctg att ccc gat tgt cat tcg tgg gct gat cag			7824
Ala Thr Leu Ser Ala Leu Ile Pro Asp Cys His Ser Trp Ala Asp Gln			

2595

2600

2605

gcc atg ccg att ccg atg ctg cgt aaa gac cgt acg gaa acc gaa act 7872
 Ala Met Pro Ile Pro Met Leu Arg Lys Asp Arg Thr Glu Thr Glu Thr
 2610 2615 2620

gtg gtc gcc gcg gtg gcg cgg gcg cac acg cgt ggt gtt ccg gtc gaa 7920
 Val Val Ala Ala Val Ala Arg Ala His Thr Arg Gly Val Pro Val Glu
 2625 2630 2635 2640

tgg tcg gcg tat ttc gcc ggc acc ggg gca cgg cgg gtc gag ttg ccg 7968
 Trp Ser Ala Tyr Phe Ala Gly Thr Gly Ala Arg Arg Val Glu Leu Pro
 2645 2650 2655

acg tat gcc ttc cag cgg cag cgg tac tgg ctg gaa aca tcg gat tac 8016
 Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Glu Thr Ser Asp Tyr
 2660 2665 2670

ggc gat gtg acg ggt atc ggc ctg gct gcg gcg gag cat ccg ttg ctg 8064
 Gly Asp Val Thr Gly Ile Gly Leu Ala Ala Ala Glu His Pro Leu Leu
 2675 2680 2685

ggg gcc gtg gtt gcg ctg gcc gat ggt gat ggg atg gtg ctg acc ggc 8112
 Gly Ala Val Val Ala Leu Ala Asp Gly Asp Gly Met Val Leu Thr Gly
 2690 2695 2700

cgg ttg tcg gtg ggg acg cat ccg tgg ctg gcc cag cat cgc gtg ctg 8160
 Arg Leu Ser Val Gly Thr His Pro Trp Leu Ala Gln His Arg Val Leu
 2705 2710 2715 2720

ggc gag gtc gtc gtc ccc ggc acc gcc atc ctg gag atg gcc ctg cac 8208
 Gly Glu Val Val Val Pro Gly Thr Ala Ile Leu Glu Met Ala Leu His
 2725 2730 2735

gca ggg gcg cgt ctc ggc tgt gac cgg gtg gaa gag ctc acc ctg gaa 8256
 Ala Gly Ala Arg Leu Gly Cys Asp Arg Val Glu Glu Leu Thr Leu Glu
 2740 2745 2750

aca ccg ctg gtg gtc ccc gaa cgc gcg gcg ggt gcc ggt agt cgt ggc 8304
 Thr Pro Leu Val Val Pro Glu Arg Ala Ala Gly Ala Gly Ser Arg Gly
 2755 2760 2765

cct gcg gga ggg acc aca gtt tca att gaa act gcg gaa gaa cgt gtg 8352
 Pro Ala Gly Gly Thr Thr Val Ser Ile Glu Thr Ala Glu Glu Arg Val
 2770 2775 2780

cgg acg aac gac gcc atc gaa atc cag ctg ctg gtg aac gca ccc gac 8400
 Arg Thr Asn Asp Ala Ile Glu Ile Gln Leu Leu Val Asn Ala Pro Asp

2785	2790	2795	2800	
gaa ggc ggt cgg cga agg gtg tcg ctg tat tcc cgc ccg gcc ggt ggg				8448
Glu Gly Gly Arg Arg Arg Val Ser Leu Tyr Ser Arg Pro Ala Gly Gly				
2805	2810	2815		
tcg aga ggt ggg ggt tgg acg cgc cac gcc acc ggc gaa ctc gtc gtc				8496
Ser Arg Gly Gly Gly Trp Thr Arg His Ala Thr Gly Glu Leu Val Val				
2820	2825	2830		
ggc acc acc ggt ggt agg gcg gtt cct gat tgg tcg gct gag ggt gcc				8544
Gly Thr Thr Gly Gly Arg Ala Val Pro Asp Trp Ser Ala Glu Gly Ala				
2835	2840	2845		
gag tcg att gct ctc gat gag ttc tac gtc gct ctg gcc gga aac ggg				8592
Glu Ser Ile Ala Leu Asp Glu Phe Tyr Val Ala Leu Ala Gly Asn Gly				
2850	2855	2860		
ttc gag tac ggg ccg ttg ttc cag ggg ctt cag gcg gca tgg cgt cgt				8640
Phe Glu Tyr Gly Pro Leu Phe Gln Gly Leu Gln Ala Ala Trp Arg Arg				
2865	2870	2875	2880	
ggt gac gag gtt ctc gcc gaa atc gcc ccg ccg gcc gag gcc gat gcg				8688
Gly Asp Glu Val Leu Ala Glu Ile Ala Pro Pro Ala Glu Ala Asp Ala				
2885	2890	2895		
atg gcg tcg gga tac ctg ctc gac cca gcg ttg ctg gat gcc gcg ctg				8736
Met Ala Ser Gly Tyr Leu Leu Asp Pro Ala Leu Leu Asp Ala Ala Leu				
2900	2905	2910		
cag gcg tcc gcg ctc ggc gac cgc ccg gag caa ggc ggc gcg tgg ctg				8784
Gln Ala Ser Ala Leu Gly Asp Arg Pro Glu Gln Gly Gly Ala Trp Leu				
2915	2920	2925		
ccg ttc tca ttc acc ggc gtc gaa ctt tcc gct ccg gca ggg acg atc				8832
Pro Phe Ser Phe Thr Gly Val Glu Leu Ser Ala Pro Ala Gly Thr Ile				
2930	2935	2940		
agc agg gtg cgg ctg gag acc agg cga ccc gac gcg ata tcg gtg gcc				8880
Ser Arg Val Arg Leu Glu Thr Arg Arg Pro Asp Ala Ile Ser Val Ala				
2945	2950	2955	2960	
gtg atg gat gag agt ggg cgg ttg ctc gcc tcg atc gat tct ctc agg				8928
Val Met Asp Glu Ser Gly Arg Leu Leu Ala Ser Ile Asp Ser Leu Arg				
2965	2970	2975		
cta cga agc gtg tcg tcg gga cag ctg gcg aat cgg gac gct gtc cgc				8976
Leu Arg Ser Val Ser Ser Gly Gln Leu Ala Asn Arg Asp Ala Val Arg				

2980

2985

2990

gac gcg ctg ttc gag gtg acc tgg gag ccg gtg gcg acg cag tcg acg 9024
 Asp Ala Leu Phe Glu Val Thr Trp Glu Pro Val Ala Thr Gln Ser Thr
 2995 3000 3005

gaa ccg ggt cgc tgg gcc ctg ctt ggt gat act gcc tgc ggt aaa gac 9072
 Glu Pro Gly Arg Trp Ala Leu Leu Gly Asp Thr Ala Cys Gly Lys Asp
 3010 3015 3020

gat ctc atc aaa ctc gca acg gat tcc gcc gac cgc tgc gcg gat ctg 9120
 Asp Leu Ile Lys Leu Ala Thr Asp Ser Ala Asp Arg Cys Ala Asp Leu
 3025 3030 3035 3040

gcg gcg cta gcc gag aaa ctt gat tcc agc gcg ctg gtt cct gat gtc 9168
 Ala Ala Leu Ala Glu Lys Leu Asp Ser Ser Ala Leu Val Pro Asp Val
 3045 3050 3055

gtg gtc tac tgc gcc gga gaa cag gcg gat ccc ggc acc ggc gca gcc 9216
 Val Val Tyr Cys Ala Gly Glu Gln Ala Asp Pro Gly Thr Gly Ala Ala
 3060 3065 3070

gca ctt gcg gag acc cag cag acg ttg gct ctg ctc caa gcg tgg ttg 9264
 Ala Leu Ala Glu Thr Gln Gln Thr Leu Ala Leu Leu Gln Ala Trp Leu
 3075 3080 3085

gct gag ccg cgg ttg gcc gag gca cgt ctg gtg gtg gtg acg tgt gca 9312
 Ala Glu Pro Arg Leu Ala Glu Ala Arg Leu Val Val Val Thr Cys Ala
 3090 3095 3100

gcg gtg acg acg gct ccg agt gac ggt gca tca gag ctg gca cat gcg 9360
 Ala Val Thr Thr Ala Pro Ser Asp Gly Ala Ser Glu Leu Ala His Ala
 3105 3110 3115 3120

ccg ttg tgg ggg ttg ttg cgt gcc gcg cag gtg gag aac ccg ggg cag 9408
 Pro Leu Trp Gly Leu Leu Arg Ala Ala Gln Val Glu Asn Pro Gly Gln
 3125 3130 3135

ttt gtg ctg gcg gac gtc gac gga acc gcc gaa tcg tgg cgt gcg ttg 9456
 Phe Val Leu Ala Asp Val Asp Gly Thr Ala Glu Ser Trp Arg Ala Leu
 3140 3145 3150

ccg agt gcg ttg ggc tcg atg gaa ccg cag ttg gcc ctg ccg aag gcc 9504
 Pro Ser Ala Leu Gly Ser Met Glu Pro Gln Leu Ala Leu Arg Lys Gly
 3155 3160 3165

gcg gtg cga gcg ccc cgc ttg gct tcg gtc gcc ggg cag atc gac gtg 9552
 Ala Val Arg Ala Pro Arg Leu Ala Ser Val Ala Gly Gln Ile Asp Val

3170	3175	3180	
ccc gcg gtt gtg gcg gat ccc gac cga acc gtg ctg att tcg ggc ggc			9600
Pro Ala Val Val Ala Asp Pro Asp Arg Thr Val Leu Ile Ser Gly Gly			
3185	3190	3195	3200
acg ggc ctg ttg ggg ggc gcg gtt gcc cgc cac ctg gtg acc gaa cgc			9648
Thr Gly Leu Leu Gly Gly Ala Val Ala Arg His Leu Val Thr Glu Arg			
3205	3210	3215	
ggt gtc cgc cga ttg gtg ttg acg ggc cgt cgt ggc tgg gat gct cct			9696
Gly Val Arg Arg Leu Val Leu Thr Gly Arg Arg Gly Trp Asp Ala Pro			
3220	3225	3230	
gga atc acc gag ttg gtg ggt gag ctg aac ggc ctc ggt gcc gtg gtc			9744
Gly Ile Thr Glu Leu Val Gly Glu Leu Asn Gly Leu Gly Ala Val Val			
3235	3240	3245	
gac gtg gtg gcg tgc gac gtc gcg gat cgt gct gat ctg gag tcg ttg			9792
Asp Val Val Ala Cys Asp Val Ala Asp Arg Ala Asp Leu Glu Ser Leu			
3250	3255	3260	
ctg gcg gcg gtc ccg gcg gaa ttt ccg ttg tgc ggc gtg gtg cat gcc			9840
Leu Ala Ala Val Pro Ala Glu Phe Pro Leu Cys Gly Val Val His Ala			
3265	3270	3275	3280
gcg ggg gcg ctg gcc gac ggg gtg atc gag tcg ttg tca ccg gac gac			9888
Ala Gly Ala Leu Ala Asp Gly Val Ile Glu Ser Leu Ser Pro Asp Asp			
3285	3290	3295	
gtg gga gcg gtg ttc ggc ccg aag gcg gcg ggg gcg tgg aat ctg cac			9936
Val Gly Ala Val Phe Gly Pro Lys Ala Ala Gly Ala Trp Asn Leu His			
3300	3305	3310	
gag ctg act cgt gat acg gac ctg tcg ttc ttc gcg ttg ttc tcc tcg			9984
Glu Leu Thr Arg Asp Thr Asp Leu Ser Phe Phe Ala Leu Phe Ser Ser			
3315	3320	3325	
ctt tcc ggt gtt gcc ggc gct cct ggt cag ggc aat tat gcg gcg gcg			10032
Leu Ser Gly Val Ala Gly Ala Pro Gly Gln Gly Asn Tyr Ala Ala Ala			
3330	3335	3340	
aac gcg ttc ctg gac gca ttg gcg cat tac cgg cgg tca cag gga ctg			10080
Asn Ala Phe Leu Asp Ala Leu Ala His Tyr Arg Arg Ser Gln Gly Leu			
3345	3350	3355	3360
cct gcg gtg tcg ctg gcc tgg ggc ctg tgg gag cag ccg agc ggg atg			10128
Pro Ala Val Ser Leu Ala Trp Gly Leu Trp Glu Gln Pro Ser Gly Met			

3365

3370

3375

acg gag acg ctc agc gag gtc gac cgg agc agg atc gcg cgc gcc aac 10176
 Thr Glu Thr Leu Ser Glu Val Asp Arg Ser Arg Ile Ala Arg Ala Asn
 3380 3385 3390

ccg ccg ttg tcc acc aag gag gga ttg cgg ctg ttc gat gcc ggg ctg 10224
 Pro Pro Leu Ser Thr Lys Glu Gly Leu Arg Leu Phe Asp Ala Gly Leu
 3395 3400 3405

gcg ctg gac cgg gca gcg gta gtt ccg gcg aag ttg gac agg act ttc 10272
 Ala Leu Asp Arg Ala Ala Val Val Pro Ala Lys Leu Asp Arg Thr Phe
 3410 3415 3420

ctg gcc gag cag gcg cgg tcg ggc tcg ctg ccc gca ttg ttg acg gca 10320
 Leu Ala Glu Gln Ala Arg Ser Gly Ser Leu Pro Ala Leu Leu Thr Ala
 3425 3430 3435 3440

ctg gta ccc ccc atc cgt cgt aat agg cgg gct agc gga acc gag ctc 10368
 Leu Val Pro Pro Ile Arg Arg Asn Arg Arg Ala Ser Gly Thr Glu Leu
 3445 3450 3455

gcg gac gag ggc acc ctg ctc ggg gtg gtg cgg gag cat gcc gcg gcc 10416
 Ala Asp Glu Gly Thr Leu Leu Gly Val Val Arg Glu His Ala Ala Ala
 3460 3465 3470

gtg ctg ggg tat tcg agc gcg gct gac gtc ggg gtc gag cgc gct ttc 10464
 Val Leu Gly Tyr Ser Ser Ala Ala Asp Val Gly Val Glu Arg Ala Phe
 3475 3480 3485

cgg gat ctg ggt ttt gat tcg ttg tct ggt gtg gag ttg cgg aac cgc 10512
 Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg Asn Arg
 3490 3495 3500

ctt gcc ggg gtg ctg ggg gtg cgg ttg ccg gcg act gcg gtg ttc gac 10560
 Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val Phe Asp
 3505 3510 3515 3520

tat ccg acg ccg agg gcg ctg gcc cgg ttc ctg cac cag gaa ctg gca 10608
 Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu Leu Ala
 3525 3530 3535

gac gag atc gct acg acg cca gcg ccg gtg acg acg acc agg gca ccg 10656
 Asp Glu Ile Ala Thr Thr Pro Ala Pro Val Thr Thr Thr Arg Ala Pro
 3540 3545 3550

gtc gcc gaa gac gat ctc gtc gcg ata gtc ggg atg gga tgc cgt ttt 10704
 Val Ala Glu Asp Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe

3555	3560	3565	
ccc ggt cag gtg tcc tcg ccg gag gag ctc tgg cgt ttg gtg gcc ggg			10752
Pro Gly Gln Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly			
3570	3575	3580	
ggc gtg gat gcg gtc gcg gac ttc cca gcc gat cgc ggc tgg gat ctg			10800
Gly Val Asp Ala Val Ala Asp Phe Pro Ala Asp Arg Gly Trp Asp Leu			
3585	3590	3595	3600
gca ggc ttg ttc gat ccg gac ccg gaa cgg gct ggg aag acc tac gtg			10848
Ala Gly Leu Phe Asp Pro Asp Pro Glu Arg Ala Gly Lys Thr Tyr Val			
3605	3610	3615	
cgg gaa ggg gcc ttc ctc acc gac gcc gat cgg ttc gat gcg ggt ttc			10896
Arg Glu Gly Ala Phe Leu Thr Asp Ala Asp Arg Phe Asp Ala Gly Phe			
3620	3625	3630	
ctc ggg att tcc ccg cgt gag gcg ttg gcg atg gat ccg cag caa cgg			10944
Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg			
3635	3640	3645	
ctg ttg ctg gag ctg tcc tgg gag gcc att gaa cgg gca ggg atc gat			10992
Leu Leu Leu Glu Leu Ser Trp Glu Ala Ile Glu Arg Ala Gly Ile Asp			
3650	3655	3660	
ccg ggt tcg ctg agg ggg agt cgg acc ggt gtg ttc gcg ggg ctg atg			11040
Pro Gly Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met			
3665	3670	3675	3680
tac cac gac tat ggc gcc cgg ttc gcc agc cga gcc ccg gaa ggt ttc			11088
Tyr His Asp Tyr Gly Ala Arg Phe Ala Ser Arg Ala Pro Glu Gly Phe			
3685	3690	3695	
gag ggg tat ctc ggc aat ggc agt gct ggg agt gtc gcg tcg ggc cgg			11136
Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Ser Val Ala Ser Gly Arg			
3700	3705	3710	
att gcg tac tcg ttt ggt ttc gag ggt cct gcg gtg acg gtg gat act			11184
Ile Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr			
3715	3720	3725	
gcg tgt tcg tcg tcg ttg gtg gcg ttg cat ttg gcg ggt cag tcg ttg			11232
Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ser Leu			
3730	3735	3740	
cgt tcc ggc gaa tgc gat ctc gcc ctt gcc ggt ggt gtg acg gtg atg			11280
Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met			

3745

3750

3755

3760

tcg acg ccc ggg acg ttt gtg gaa ttc tcc cgt cag cgg ggc ctg gca 11328
 Ser Thr Pro Gly Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala
 3765 3770 3775

ccg gac ggg cgg tgc aag tcg ttc gcg gag agc gcg gac ggt acc ggt 11376
 Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala Asp Gly Thr Gly
 3780 3785 3790

tgg ggt gag ggt gct ggt ttg gtg ttg ttg gag cgg ttg tcg gat gct 11424
 Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala
 3795 3800 3805

cgg cgg aat ggg cat cgg gtg ttg gcg gtg gtt cgt ggg tcg gcg gtg 11472
 Arg Arg Asn Gly His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val
 3810 3815 3820

aat cag gat ggt gcg tcg aat ggc ttg acc gcg ccg aat ggt ccc tcg 11520
 Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
 3825 3830 3835 3840

cag cag cgg gtc atc cag cag gcg ttg gcg agt gcg ggt ctg tcg gtg 11568
 Gln Gln Arg Val Ile Gln Gln Ala Leu Ala Ser Ala Gly Leu Ser Val
 3845 3850 3855

tcc gat gtg gat gcc gtg gag gcg cat ggg acc ggg acc agg ttg ggt 11616
 Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly
 3860 3865 3870

gat ccg att gag gcg cag gct ctg att gct acg tat ggg cgc gat cgt 11664
 Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg
 3875 3880 3885

gat ccc ggt cgg ccg ttg tgg ttg ggg tcg gtg aag tcc aac atc ggt 11712
 Asp Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly
 3890 3895 3900

cat acg cag gcg gcg gcg ggt gtt gcc ggt gtg atc aag atg gtg atg 11760
 His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met
 3905 3910 3915 3920

gcg atg cgg cac ggg caa ctt ccg cgc acg ctg cac gtg gat gca ccc 11808
 Ala Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Asp Ala Pro
 3925 3930 3935

tcc tcg cag gtg gat tgg tcg gcg ggg agg gtc cag ctc ctg acg gag 11856
 Ser Ser Gln Val Asp Trp Ser Ala Gly Arg Val Gln Leu Leu Thr Glu

3940	3945	3950	
aac acg ccc tgg ccc gac agt ggt cgc ccc tgt cgg gtg ggg gtg tcg			11904
Asn Thr Pro Trp Pro Asp Ser Gly Arg Pro Cys Arg Val Gly Val Ser			
3955	3960	3965	
tcg ttc ggg atc agc ggc acc aac gcg cac gtc atc ctg gaa cag tcc			11952
Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Ser			
3970	3975	3980	
acg ggg cag atg gat cag gca gcg gag ccg gat tcg agt cct gtt ctg			12000
Thr Gly Gln Met Asp Gln Ala Ala Glu Pro Asp Ser Ser Pro Val Leu			
3985	3990	3995	4000
gat gtt ccg gtg gtg ccg tgg gtg gtg tcg ggc aaa aca ccc gaa gcg			12048
Asp Val Pro Val Val Pro Trp Val Val Ser Gly Lys Thr Pro Glu Ala			
4005	4010	4015	
cta tcc gcc cag gcg gca acg ttg gcg acc tat ttg gac caa aat gtt			12096
Leu Ser Ala Gln Ala Ala Thr Leu Ala Thr Tyr Leu Asp Gln Asn Val			
4020	4025	4030	
gat gtc tcc cct ctg gac gtt ggg att tcg ctt gcg gtg acc cgt tcg			12144
Asp Val Ser Pro Leu Asp Val Gly Ile Ser Leu Ala Val Thr Arg Ser			
4035	4040	4045	
gcg ctg gat gag ccg gcg gtg gtg ctg ggg tcg gat cgt gac acg ttg			12192
Ala Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Asp Thr Leu			
4050	4055	4060	
ttg tct ggc ctg aat gcg ctg gct gcc ggt cat gag gct gct ggc gtg			12240
Leu Ser Gly Leu Asn Ala Leu Ala Ala Gly His Glu Ala Ala Gly Val			
4065	4070	4075	4080
gtt acg gga cct gtc ggg att ggt ggc ccg acc ggg ttt gtg ttc gcc			12288
Val Thr Gly Pro Val Gly Ile Gly Gly Arg Thr Gly Phe Val Phe Ala			
4085	4090	4095	
ggt caa ggc ggt cag tgg ttg ggg atg ggc cgc ccg ttg tac tcg gag			12336
Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Arg Leu Tyr Ser Glu			
4100	4105	4110	
ttt ccg gcg ttc gcc ggt gct ttc gac gaa gca tgc gcc gag ctc gat			12384
Phe Pro Ala Phe Ala Gly Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp			
4115	4120	4125	
gcg aac ctg ggg agg gaa gtc ggg gtt ccg gat gtg gtg ttc ggc tcc			12432
Ala Asn Leu Gly Arg Glu Val Gly Val Arg Asp Val Val Phe Gly Ser			

4130	4135	4140	
gac gag tcc ttg ctg gat cgg act ttg tgg gcg cag tcg ggt ttg ttc			12480
Asp Glu Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser Gly Leu Phe			
4145	4150	4155	4160
gcg ttg cag gtc ggt ctc tgg gaa ttg ttg ggt acg tgg ggt gtt cgg			12528
Ala Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Thr Trp Gly Val Arg			
4165	4170	4175	
ccc agc gta gtg ctg ggg cat tcg gtc ggg gag cta gcc gcg gcg ttc			12576
Pro Ser Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe			
4180	4185	4190	
gcc gca ggt gtg ctg tcg atg gcg gag gcg gct cgg ctg gtg gcg ggt			12624
Ala Ala Gly Val Leu Ser Met Ala Glu Ala Ala Arg Leu Val Ala Gly			
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cgt gcg cgg ttg atg cag gcg ttg cct tct ggc ggt gcc atg ctg gcg			12672
Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala Met Leu Ala			
4210	4215	4220	
gtg tcc gcg acc gag gcc cga gtc ggc ccg ctg ctc gat ggg gtg cgg			12720
Val Ser Ala Thr Glu Ala Arg Val Gly Pro Leu Leu Asp Gly Val Arg			
4225	4230	4235	4240
gat cgt gtt ggt gtc gca gcg gtt aac gct ccg ggg tcg gtg gtg ctt			12768
Asp Arg Val Gly Val Ala Ala Val Asn Ala Pro Gly Ser Val Val Leu			
4245	4250	4255	
tcc ggt gac cgg gat gtg ctc gat ggc att gcc ggt cgg ctg gac ggg			12816
Ser Gly Asp Arg Asp Val Leu Asp Gly Ile Ala Gly Arg Leu Asp Gly			
4260	4265	4270	
caa ggt atc cgg tcg agg tgg ttg cgg gtt tcg cac gcg ttt cat tcg			12864
Gln Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser			
4275	4280	4285	
cat cgg atg gat ccg atg ctg gcg gag ttc gcc gag ctc gca cgg agc			12912
His Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Ser			
4290	4295	4300	
gtg gac tac cgg tct cca cgg ctg ccg att gtc tcg acg ctg acc gga			12960
Val Asp Tyr Arg Ser Pro Arg Leu Pro Ile Val Ser Thr Leu Thr Gly			
4305	4310	4315	4320
aac ctc gat gac gtg ggc gtg atg gct acg ccg gag tat tgg gtg cgc			13008
Asn Leu Asp Asp Val Gly Val Met Ala Thr Pro Glu Tyr Trp Val Arg			

4325	4330	4335	
cag gtg cga gag ccc gtc cgc ttc gcc gac ggt gtc cag gcg ctt gtg			13056
Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val			
4340	4345	4350	
gac caa ggc gtc gac acg att gtg gaa ctc ggt ccg gac ggg gcg ttg			13104
Asp Gln Gly Val Asp Thr Ile Val Glu Leu Gly Pro Asp Gly Ala Leu			
4355	4360	4365	
tcg agc ttg gtt caa gag tgt gtg gcg gag tcc ggg cgg gcg acg ggg			13152
Ser Ser Leu Val Gln Glu Cys Val Ala Glu Ser Gly Arg Ala Thr Gly			
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att ccg ttg gtg cgg aga gac cgt gat gag gtc cga acg gtg ctg gac			13200
Ile Pro Leu Val Arg Arg Asp Arg Asp Glu Val Arg Thr Val Leu Asp			
4385	4390	4395	4400
gct ttg gcg cag acc cac act cgt ggt ggc gcg gtg gac tgg ggg tca			13248
Ala Leu Ala Gln Thr His Thr Arg Gly Gly Ala Val Asp Trp Gly Ser			
4405	4410	4415	
ttt ttc gct ggt acg agg gca acg caa gtc gac ctt ccc acg tat gcc			13296
Phe Phe Ala Gly Thr Arg Ala Thr Gln Val Asp Leu Pro Thr Tyr Ala			
4420	4425	4430	
ttc caa cga cag cgg tac tgg ctg gag cca tcg gat tcc ggt gat gtg			13344
Phe Gln Arg Gln Arg Tyr Trp Leu Glu Pro Ser Asp Ser Gly Asp Val			
4435	4440	4445	
acc ggt gtt ggc ctg acc ggg gcg gag cat ccg ctg ttg ggt gcc gtg			13392
Thr Gly Val Gly Leu Thr Gly Ala Glu His Pro Leu Leu Gly Ala Val			
4450	4455	4460	
gtg ccg gtc gcg ggc ggc gat gag gtg ctg ctg acc ggc agg ctg tcg			13440
Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg Leu Ser			
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gtg ggg acg cat ccg tgg ctg gcg gaa cac cgc gtg ctg ggc gaa gtc			13488
Val Gly Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly Glu Val			
4485	4490	4495	
gtc gtc ccc ggc acc gcg ttg ctg gag atg gcg tgg cgg gcc ggt agc			13536
Val Val Pro Gly Thr Ala Leu Leu Glu Met Ala Trp Arg Ala Gly Ser			
4500	4505	4510	
cag gtc ggt tgt gaa cgt gtg gag gag ctc acc ttg gag gca ccg ctg			13584
Gln Val Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala Pro Leu			

4515

4520

4525

gtc ctg ccg gag cgg ggc gct gcg gcg gtg cag ttg gcg gtg ggg gct 13632
 Val Leu Pro Glu Arg Gly Ala Ala Val Gln Leu Ala Val Gly Ala
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 Pro Asp Glu Ala Gly Arg Arg Ser Leu Gln Leu Tyr Ser Arg Gly Ala
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 Asp Glu Asp Gly Asp Trp Arg Arg Ile Ala Ser Gly Leu Leu Ala Gln
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 Ala Asn Ala Val Pro Pro Ala Asp Ser Thr Ala Trp Pro Pro Asp Gly
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 Ala Gly Gln Val Asp Leu Ala Glu Phe Tyr Glu Arg Leu Ala Glu Arg
 4595 4600 4605

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 Gly Leu Thr Tyr Gly Pro Val Phe Gln Gly Leu Arg Ala Ala Trp Arg
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cac ggc gac gat atc ttc gcc gaa ttg gcc ggg tca cca gac gcc tcg 13920
 His Gly Asp Asp Ile Phe Ala Glu Leu Ala Gly Ser Pro Asp Ala Ser
 4625 4630 4635 4640

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 Gly Phe Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu His Ala Met
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gcg ctt ggt gct tcg ccc gac tcg gaa gcg cgt ctg ccg ttt tcc tgg 14016
 Ala Leu Gly Ala Ser Pro Asp Ser Glu Ala Arg Leu Pro Phe Ser Trp
 4660 4665 4670

cgt ggc gcc cag ctg tac cgc gct gaa gga gca gcg ctt cgg gta cgg 14064
 Arg Gly Ala Gln Leu Tyr Arg Ala Glu Gly Ala Ala Leu Arg Val Arg
 4675 4680 4685

ctc tcg ccg ctg ggc tcc ggt gca gtc tca ttg acg ttg gtg gat gcc 14112
 Leu Ser Pro Leu Gly Ser Gly Ala Val Ser Leu Thr Leu Val Asp Ala
 4690 4695 4700

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 Thr Gly Arg Arg Val Ala Ala Val Glu Ser Leu Ser Thr Arg Pro Val

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Ser Thr Asp Gln Ile Gly Ala Gly Arg Gly Asp Gln Glu Arg Leu Leu				
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His Val Glu Trp Val Arg Ser Ala Glu Ser Ala Gly Met Ser Leu Thr				
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Ser Cys Ala Val Val Gly Leu Gly Glu Pro Glu Trp His Ala Ala Leu				
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Lys Thr Thr Gly Val Gln Val Glu Ser His Ala Asp Leu Ala Ser Leu				
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gcc acc gag gtt gcc aag cgg ggt tca gct cct ggt gcg gtc atc gtc				14400
Ala Thr Glu Val Ala Lys Arg Gly Ser Ala Pro Gly Ala Val Ile Val				
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ccg tgc ccg cga ccc cga gcg atg cag gag ctg ccg acc gcc gcg cga				14448
Pro Cys Pro Arg Pro Arg Ala Met Gln Glu Leu Pro Thr Ala Ala Arg				
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Arg Ala Thr Gln Gln Ala Met Ala Met Leu Gln Gln Trp Leu Ala Asp				
4820	4825		4830	
gac cgg ttc gtc agt acg cgc ctg atc ctg ctg acg cat cgg gcg gtc				14544
Asp Arg Phe Val Ser Thr Arg Leu Ile Leu Leu Thr His Arg Ala Val				
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Ser Ala Val Ala Gly Glu Asp Val Leu Asp Leu Val His Ala Pro Leu				
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Trp Gly Leu Val Arg Ser Ala Gln Ala Glu His Pro Asp Arg Phe Ala				
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Leu Ile Asp Met Asp Asp Glu Arg Ala Ser Gln Thr Ala Leu Ala Glu				
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Ala Leu Thr Ala Gly Glu Ala Gln Leu Ala Val Arg Ser Gly Val Val				

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Arg Trp Asp Glu Gly Thr Val Leu Val Thr Gly Gly Thr Gly Gly Leu			
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Gly Ala Leu Leu Ala Arg His Leu Val Ser Ala His Gly Val Arg His			
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Leu Leu Leu Ala Ser Arg Arg Gly Leu Ala Ala Pro Gly Ala Asp Glu			
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Pro Ala Glu Asn Pro Leu Arg Val Val Val His Ala Ala Gly Val Leu			
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Asp Asp Gly Val Leu Met Ser Met Ser Pro Glu Arg Leu Asp Ala Val			
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Leu Arg Pro Lys Val Asp Ala Ala Trp Tyr Leu His Glu Leu Thr Arg			
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Glu Leu Gly Leu Ser Ala Phe Val Leu Phe Ser Ser Val Ala Gly Leu			
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<212> PRT

<213> Saccharopolyspora spinosa

<400> 50

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 35 40 45

Val Ser Thr Pro Glu Glu Leu Trp Arg Leu Val Val Asp Gly Gly Asp
 50 55 60

Ala Ile Ala Asn Phe Pro Glu Asp Arg Gly Trp Asn Leu Asp Glu Leu
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Phe Asp Pro Asp Pro Gly Arg Ala Gly Thr Ser Tyr Val Arg Glu Gly
85 90 95

Gly Phe Leu Arg Gly Val Ala Asp Phe Asp Ala Gly Leu Phe Gly Ile
100 105 110

Ser Pro Arg Glu Ala Gln Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
115 120 125

Glu Ile Ser Trp Glu Val Phe Glu Arg Ala Gly Ile Asp Pro Phe Ser
130 135 140

Leu Arg Gly Thr Lys Thr Gly Val Phe Ala Gly Leu Ile Tyr His Asp
145 150 155 160

Tyr Ala Ser Arg Phe Arg Lys Thr Pro Ala Glu Phe Glu Gly Tyr Phe
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Ala Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Thr
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Phe Gly Leu Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser
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Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Leu Gly Glu
210 215 220

Cys Asp Leu Ala Leu Ala Gly Gly Ile Ser Val Met Ala Thr Pro Gly
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Cys Lys Pro Phe Ala Asp Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
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Thr Ser Asn Gly Leu Thr Ala Pro Ser Gly Pro Ala Gln Gln Arg Val
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Ile Arg Gln Ala Leu Ala Asn Ala Gly Leu Ser Pro Ala Glu Val Asp
325 330 335

Val Val Glu Ala His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu
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Pro Asp Leu Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Met
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Gly Lys Thr Glu Thr Ala Leu Arg Glu Gln Ala Ala Glu Leu Leu Ser
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Val Val Thr Glu His Pro Glu Pro Gly Leu Gly Asp Val Gly Tyr Ser
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675 680 685

Gly Gly Met Leu Ala Ile Ala Leu Pro Glu Ser Ala Val Val Lys Arg
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Glu Leu Thr Ala Glu Asn Val Gln Thr Arg Arg Val Gly Ile Asp Tyr
740 745 750

Ala Ser His Ser Pro Gln Ile Ala Gln Val Gln Gly Arg Leu Leu Asp
755 760 765

Arg Leu Gly Glu Val Gly Ser Glu Pro Ala Glu Ile Ala Phe Tyr Ser
770 775 780

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Tyr Asp Ala Gly Asp Leu Gly Ser Val Gly Leu Leu Ser Ala Glu His
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Pro Leu Leu Gly Ala Ala Val Thr Leu Ala Asp Ala Gly Gly Phe Leu
930 935 940

Leu Thr Gly Lys Leu Ser Val Lys Thr Gln Pro Trp Leu Ala Asp His
945 950 955 960

Val Val Gly Gly Ala Ile Leu Leu Pro Gly Thr Ala Phe Val Glu Met
965 970 975

Leu Ile Arg Ala Ala Asp Gln Val Gly Cys Asp Leu Ile Glu Glu Leu
980 985 990

Ser Leu Thr Thr Pro Leu Val Leu Pro Ala Thr Gly Ala Val Gln Val
995 1000 1005

Gln Ile Ala Val Gly Gly Pro Asp Glu Ala Gly Arg Arg Ser Val Arg
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Val His Ser Cys Arg Asp Asp Ala Val Pro Gln Asp Ser Trp Thr Cys
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His Ala Thr Gly Thr Leu Thr Ser Ser Asp His Gln Asp Ala Gly Gln
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Gly Pro Asp Gly Ile Trp Pro Pro Asn Asp Ala Val Ala Val Pro Leu
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Asp Ser Phe Tyr Ala Arg Ala Ala Glu Arg Gly Phe Asp Phe Gly Pro
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Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu Gln Ala Leu Gly Ala
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Ala Glu Glu Asp Pro Asp Glu Gly Trp Leu Pro Phe Ala Trp Gln Gly
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Val Ser Leu Lys Ala Thr Gly Ala Leu Ser Leu Arg Val His Leu Val
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Pro Ala Gly Ala Asn Ala Val Ser Val Phe Thr Thr Asp Thr Thr Gly
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Gln Ala Val Leu Ser Ile Asp Ser Leu Val Leu Arg Gln Ile Ser Asp
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Lys Gln Leu Ala Ala Ala Arg Ala Met Glu His Glu Ser Leu Phe Arg
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Val Asp Trp Lys Arg Ile Ser Pro Gly Ala Ala Lys Pro Val Ser Trp
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 1250 1255 1260

Asp Val Val Val Val Pro Cys Gly Ala Ser Arg Gln Asp Leu Asp Val
 265 1270 1275 1280

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Asp Trp Leu Ala Ala Ala Arg Phe Ala Gly Ser Arg Leu Val Val Val
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Val His Ala Ala Gly Ala Leu Ala Asp Gly Val Val Glu Ser Leu Thr
1490 1495 1500

Pro Glu His Val Ala Lys Val Phe Gly Pro Lys Ala Ala Gly Ala Trp
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His Leu His Glu Leu Thr Leu Asp Leu Asp Leu Ser Phe Phe Val Leu
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Phe Ser Ser Phe Ser Gly Val Ala Gly Ala Ala Gly Gln Gly Asn Tyr
1540 1545 1550

Ala Ala Ala Asn Ala Phe Leu Asp Gly Leu Ala Gln His Arg Arg Thr
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Ala Gly Leu Pro Ala Val Ser Leu Ala Trp Gly Leu Trp Glu Gln Pro
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Ser Gly Met Thr Gly Ala Leu Asp Ala Ala Gly Arg Ser Arg Ile Ala
1585 1590 1595 1600

Arg Thr Asn Pro Pro Met Ser Ala Pro Asp Gly Leu Arg Leu Phe Glu
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Met Ala Phe Arg Val Pro Gly Glu Ser Leu Leu Val Pro Val His Val
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Asp Leu Asn Ala Leu Arg Ala Asp Ala Ala Asp Gly Gly Val Pro Ala
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Glu Ser Ala Asp Val Asn Gly Leu Val Gly Arg Leu Arg Arg Leu Pro
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Asp Leu Asp Gln Glu Thr Gln Leu Leu Gly Leu Val Arg Glu His Val
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Ser Ala Val Leu Gly His Ser Gly Ala Val Glu Val Gly Ala Asp Arg
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Asn Arg Leu Gly Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val
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Phe Asp Tyr Pro Thr Pro Arg Ala Leu Val Arg Phe Leu Leu Asp Lys
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Gly Gly Leu Asp Ala Val Ala Glu Phe Pro Asp Asp Arg Gly Trp Asp
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Gln Ala Gly Leu Phe Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr
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Val Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Gly
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Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln
1860 1865 1870
Arg Leu Leu Leu Glu Val Ala Trp Glu Thr Val Glu Arg Ala Gly Ile
1875 1880 1885
Asp Pro Leu Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu
1890 1895 1900
Met His His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly
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Phe Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Gly Val Phe Ser Gly
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Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp
1940 1945 1950
Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala
1955 1960 1965
Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val
1970 1975 1980
Met Ala Thr Pro Gly Met Phe Val Glu Phe Ser Arg Gln Arg Gly Leu
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2005 2010 2015
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Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly
2100 2105 2110

Arg Asp Ser Asp Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile
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Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val
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Met Ala Met Arg His Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu
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Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala
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Asp Arg Val Asp Gly Ala Gly Ile Ala Ala Val Asn Ala Pro Glu Ser
465 2470 2475 2480

Val Val Leu Ser Gly Asp Arg Glu Val Leu Asp Asp Ile Ala Gly Ala
2485 2490 2495

Leu Asp Gly Gln Gly Ile Arg Trp Arg Arg Leu Arg Val Ser His Ala
2500 2505 2510

Phe His Ser Tyr Arg Met Asp Pro Met Leu Gln Glu Phe Ala Glu Ile
2515 2520 2525

Ala Arg Ser Val Asp Tyr Arg Arg Gly Asp Leu Pro Val Val Ser Thr
2530 2535 2540

Leu Thr Gly Glu Leu Asp Thr Ala Gly Val Met Ala Thr Pro Glu Tyr
545 2550 2555 2560

Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Arg
2565 2570 2575

Val Leu Ala Gln Gln Gly Val Ala Thr Ile Phe Glu Leu Gly Pro Asp
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Gly Ala Val Val Ala Leu Ala Asp Gly Asp Gly Met Val Leu Thr Gly
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Ala Gly Ala Arg Leu Gly Cys Asp Arg Val Glu Glu Leu Thr Leu Glu
2740 2745 2750

Thr Pro Leu Val Val Pro Glu Arg Ala Ala Gly Ala Gly Ser Arg Gly
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Pro Ala Gly Gly Thr Thr Val Ser Ile Glu Thr Ala Glu Glu Arg Val
2770 2775 2780

Arg Thr Asn Asp Ala Ile Glu Ile Gln Leu Leu Val Asn Ala Pro Asp
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Glu Gly Gly Arg Arg Arg Val Ser Leu Tyr Ser Arg Pro Ala Gly Gly
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Ser Arg Gly Gly Gly Trp Thr Arg His Ala Thr Gly Glu Leu Val Val
2820 2825 2830

Gly Thr Thr Gly Gly Arg Ala Val Pro Asp Trp Ser Ala Glu Gly Ala
2835 2840 2845

Glu Ser Ile Ala Leu Asp Glu Phe Tyr Val Ala Leu Ala Gly Asn Gly
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Phe Glu Tyr Gly Pro Leu Phe Gln Gly Leu Gln Ala Ala Trp Arg Arg
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Cys Asp Ser Ala Asp Arg Asp Ser Leu Ala Arg Leu Val Ala Ser V
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cggcggagcc ggtttcatcg gctcgcaacta cgcttcggcag ttgctcgggtg gtgcg
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 Val Val Val Leu Asp Lys Leu Thr Tyr Ala Gly Asn Glu Ala Asn Le
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Ala Pro Val Ala Asp Asn Pro Arg Leu Lys Phe Val Cys Gly Asp
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Cys Asp Arg Glu Leu Val Gly Gly Leu Met Ser Gly Val Asp Val
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Val His Phe Ala Ala Glu Thr His Val Asp Arg Ser Ile Thr Gly
85 90 95

Asp Ala Phe Val Ile Thr Asn Val Val Gly Thr Asn Val Leu Leu
100 105 110

Ala Ala Leu Asp Ala Glu Ile Gly Lys Phe Val His Val Ser Thr
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130 135 140

Leu Glu Pro Asn Ser Pro Tyr Ser Ala Ala Lys Ala Gly Ser Asp
145 150 155

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165 170 175

Arg Cys Ser Asn Asn Tyr Gly Pro Tyr Gln Phe Pro Glu Lys Val
180 185 190

Pro Leu Phe Ile Thr Asn Leu Met Asp Gly Ser Gln Val Pro Leu
195 200 205

Gly Asp Gly Leu Asn Val Arg Asp Trp Leu His Val Ser Asp His
210 215 220

Arg Gly Ile Gln Leu Val Ala Asp Ser Gly Arg Ala Gly Glu Ile
225 230 235

Asn Ile Gly Gly Gly Thr Glu Leu Thr Asn Asn Glu Leu Thr Glu
245 250 255

Leu Leu Ala Glu Leu Gly Leu Asp Trp Ser Val Val Arg Pro Val
260 265 270

Asp Arg Lys Gly His Asp Arg Arg Tyr Ser Val Asp His Ser Lys
275 280 285

Val Glu Glu Leu Gly Tyr Ala Pro Gln Val Asp Phe Glu Thr Gly
290 295 300

Thr Asp Tyr Val Phe Pro Asp Gly Ala Arg Pro Tyr Glu Pro
 115 120 125

gac ccg acc ggg ccg cga tgc gtc tac ggg cgc acc aag ctc gaa
 Asp Pro Thr Gly Pro Arg Ser Val Tyr Gly Arg Thr Lys Leu Glu
 130 135 140

gaa cgg gcc gtg ctg gag tcc ggc gcg cgg gcc tgg gtg gtg cgc
 Glu Arg Ala Val Leu Glu Ser Gly Ala Arg Ala Trp Val Val Arg
 145 150 155

gca tgg gtg tac ggc gcg agc ggc aag aac ttc ctg aaa acg atg
 Ala Trp Val Tyr Gly Ala Ser Gly Lys Asn Phe Leu Lys Thr Met
 165 170 175

cgc ctc tgc ggg gag cgc gac acg ctg tcc gtt gtg gac gat cag
 Arg Leu Ser Gly Glu Arg Asp Thr Leu Ser Val Val Asp Asp Gln
 180 185 190

ggc tgc ccg act tgg gcg gcg gac ctg gcg agc ggc ctg ctg gag
 Gly Ser Pro Thr Trp Ala Ala Asp Leu Ala Ser Gly Leu Leu Glu
 195 200 205

gcc gaa cgg gtc gcc gaa cgc cgt gga ccg gag cag aag gtg ctg
 Ala Glu Arg Val Ala Glu Arg Arg Gly Pro Glu Gln Lys Val Leu
 210 215 220

tgc acc aat tcc ggc cag gtg acc tgg tac gag ttc gcg cgg gcg
 Cys Thr Asn Ser Gly Gln Val Thr Trp Tyr Glu Phe Ala Arg Ala
 225 230 235

ttc gcg gaa ttc ggc ctg gac gag aac cgc gtc cac ccg tgc acg
 Phe Ala Glu Phe Gly Leu Asp Glu Asn Arg Val His Pro Cys Thr
 245 250 255

gcg gac ttc ccc ctc ccg gcg cac cgc ccg gcc tac tgc gtc ctg
 Ala Asp Phe Pro Leu Pro Ala His Arg Pro Ala Tyr Ser Val Leu
 260 265 270

gac gtg gcg tgg cga gag gcg ggc ctg acc ccg atg cgc acc tgg
 Asp Val Ala Trp Arg Glu Ala Gly Leu Thr Pro Met Arg Thr Trp
 275 280 285

gaa gcc ctg gcg gcg gcc ttc gag aaa gac ggc gaa acc ctc cga
 Glu Ala Leu Ala Ala Ala Phe Glu Lys Asp Gly Glu Thr Leu Arg
 290 295 300

cgc tga

Ala Glu Arg Val Ala Glu Arg Arg Gly Pro Glu Gln Lys Val Leu
210 215 220

Cys Thr Asn Ser Gly Gln Val Thr Trp Tyr Glu Phe Ala Arg Ala
225 230 235

Phe Ala Glu Phe Gly Leu Asp Glu Asn Arg Val His Pro Cys Thr
245 250 255

Ala Asp Phe Pro Leu Pro Ala His Arg Pro Ala Tyr Ser Val Leu
260 265 270

Asp Val Ala Trp Arg Glu Ala Gly Leu Thr Pro Met Arg Thr Trp
275 280 285

Glu Ala Leu Ala Ala Ala Phe Glu Lys Asp Gly Glu Thr Leu Arg
290 295 300

Arg
305

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